Clinical Summary

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Laser Angioplasty for Critical Limb Ischemia
Phase 2
(LACI 2)

A multicenter registry of peripheral excimer laser-assisted angioplasty for the treatment of chronic critical limb ischemia in poor surgical candidates

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1. Structured Abstract: LACI Phase 2

Conclusions: Despite containing a more morbid patient set, the Registry Group experienced slightly higher limb salvage rate than the Control. Overall survival at 6 months was similar, tending to favor the Registry Group. As hypothesized in the protocol, the Registry Group demonstrated equivalence to the benchmark values provided by the Control Group while requiring 35% fewer surgical procedures during the course of the study.

Investigators: Twelve U.S. sites and three German sites enrolled patients in this registry.

Purpose: To determine whether excimer laser ablation of vascular obstructions, with or without adjunctive balloon angioplasty, can prevent amputations above the ankle and relieve chronic limb ischemia (CLI). The primary effectiveness measure was limb salvage (freedom from major amputation) at 6 months; the primary safety measure was survival at 6 months.

Design: A multicenter prospective registry of peripheral excimer laser-assisted atherectomy for the treatment of CLI in poor surgical candidates. The historical control used is the Control Group of a randomized trial of prostaglandin in CLI patients described in Ann Intern Med 1999; 130:412-421.

Demography: 160 patients were enrolled. The Training Group contained 15 patients, and the pivotal Registry Group contained 155 limbs of 145 patients, in which mean patient age was 72 ? 10 years (range 45 - 91) with 53% men. The Registry Group had more comorbid disease, less history of smoking, and fewer men than the Control Group.

Methods: Patients with CLI (Rutherford Category 4-6) were prospectively enrolled. The patients had culprit lesions in the superficial femoral artery (SFA), popliteal, and/or infrapopliteal arteries, with at least one angiographically identifiable below-the-knee artery, while being poor surgical candidates, indicated by at least one of the following conditions: (a) absence of venous autologous grafts; (b) poor (diffusely diseased or <1mm diameter) or no distal vessels available for graft anastamosis; (c) high risk of surgical mortality, evidenced by American Society of Anesthesiologists Physical Class 4 or higher. Patients received intravascular treatment, including guidewire canalization, excimer laser atherectomy, balloon angioplasty, and optional stenting. The primary endpoint was limb salvage (freedom from amputation above the ankle). Secondary endpoints included death, persistent CLI, frequency of bypass surgery, and other events.

Table 1 Primary Safety and Efficacy Endpoints

	Registry Group n (%)	Control n (%)	Difference[95% CI]
Patients	145 (100%)	673 (100%)	
Primary Endpoint (note 1)	110 (76%)	494 (73%)	2.5% [-5.7% , 10.6%]
Death, any cause	15 (10%)	96 (14%)	-3.9% [-9.5% , 1.7%]

NOTES:

1. Patients without major amputation, death, lost-to-follow-up, or withdrawal
2. Difference = LACI-Control = p1-p2. SEM=(p1q1/n1 + p2q2/n2). D=SEM*1.96. Corr= (1/n1 + 1/n2)/2. Lo=Difference-D-Corr. Hi=Difference+D+Corr.

2. Figure and Table Index

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3. Definitions

All Patients all patients enrolled in LACI Phase 2

Ankle-brachial index (ABI) blood pressure at the ankle was measured with a Doppler probe; the highest tibial pressure value measured for each leg was chosen for calculation of ABI. The highest of the two brachial measurements was used as the denominator to calculate ABI = tibial pressure/brachial pressure. If it was believed that the vessels of the lower limb were calcified or the result of the ankle pressure measurement was expected to be falsely positive, this was noted on the Case Report Form.

Acute limb ischemia (ALI) any form of (leg) ischemia that requires immediate therapy whether this is with thrombolysis or any reintervention (PTA or surgery) during the concurrent hospitalization or during follow-up.

AKA above-the-knee amputation, a major amputation

ASA Physical Class American Society of Anesthesiologists Physical Class

ASA Class	Description	Examples
1	A normal, healthy patient, without organic, physiologic, or psychiatric disturbance	Healthy with good exercise tolerance
2	A patient with controlled medical conditions without significant systemic effects	Controlled hypertension, controlled diabetes mellitus without system effects, cigarette smoking without evidence of COPD, anemia, mild obesity, ages less than 1 or greater than 70 years, pregnancy
3	A patient having medical conditions with significant systemic effects intermittently associated with significant functional compromise	Controlled CHF, stable angina, old MI, poorly controlled hypertension, morbid obesity, bronchospastic disease with intermittent symptoms, chronic renal failure
4	A patient with a medical condition that is poorly controlled, associated with significant dysfunction and is a potential threat to life	Unstable angina, symptomatic COPD, symptomatic CHF, hepatorenal failure
5	A patient with a critical medical condition that is associated with little chance of survival with or without the surgical procedure	Multiorgan failure, sepsis syndrome with hemodynamic instability, hypothermia, poorly controlled coagulopathy
6	A patient who is brain dead and undergoing anesthesia care for the purposes of organ donation	
E	This modifier is added to any of the above classes to signify a procedure that is being performed as an emergency and may be associated with a suboptimal opportunity for risk modification	

BKA below-the-knee amputation, a major amputation

Category 4 Legs subgroup of Registry Legs that presented with rest pain only (that is, Rutherford Category 4)

Category 5-6 Legs subgroup of Registry Legs that presented with Rutherford Category 5 or 6 (ulcerations and/or gangrene, or minor amputation required)

CLI Chronic Critical Limb Ischemia. Used to describe patients presenting with chronic (at least two weeks duration) ischemic rest pain, ulcers or gangrene, i.e. Rutherford category 4, 5, or 6

Clinical Success absence of major amputation at six months, i.e. Limb Salvage, equivalent to the Primary Endpoint

Complication periprocedural event including spasm, thrombus, acute recoil, perforation, major dissection, distal embolization, or other event requiring additional therapy

Control Group the Control Group patients in the randomized trial reported in:
ICAI Study Group. Prostanoids for Chronic Critical Leg Ischemia: a randomized, controlled, open-label trial with Prostaglandin E1. Ann Intern Med 1999; 130:412-421

CVX-300 laser the model CVX-300 excimer laser system is a XeCl laser that emits pulses of ultraviolet light at 308 nm. The system accommodates a variety of fiberoptic catheters, including those designed for coronary atherectomy, peripheral atherectomy, and pacing lead removal. Operating parameter ranges are fluence between 30 and 60 mJ/mm^2 and pulse repetition rates between 25 and 80 pulses per second. The CVX-300 was given PMA in 1993 for coronary atherectomy and in 1997 for pacing lead removal.

ELA Excimer Laser (peripheral) Atherectomy

ELCA Excimer Laser Coronary Atherectomy

Excimer a contraction of "excited dimer." Excimer lasers are a class of gas-discharge lasers, in which pulsed high-energy electrical current is passed through a gas mixture. In excimer lasers, the mixture contains a rare gas (Ar, Kr, or Xe) and a halogen (Cl or F). The wavelength of the emitted light is determined by which rare gas-halogen pair are in the mixture. Most excimer lasers emit in the ultraviolet region, generally between 350 and 193 nm.

Exclusion criteria

- ?? Age below 18 years
- ?? Pregnancy, or plan to become pregnant
- ?? Participation in another cardiovascular or peripheral vascular IDE study.
- ?? Myocardial infarction (MI) in prior month
- ?? Stents at treatment site
- ?? Disorders or allergies precluding use of radiographic contrast
- ?? Renal insufficiency severe enough to contraindicate use of radiographic contrast
- ?? Contraindication to treatment with anticoagulants
- ?? Untreated ipsilateral iliac stenosis >70%
- ?? Inability or unwillingness of the patient to comply with intended examinations.
- ?? Unavailability of required procedural or imaging equipment
- ?? Lesion located in a graft
- ?? Hemodynamically significant arrhythmia or left ventricular ejection fraction <20%

- ?? Life expectancy less than 6 months
- ?? Necrosis necessitating major amputation

Fluence ultraviolet energy emitted by the tip of a laser catheter divided by the total area of all optical fibers in the catheter. For instance, if a catheter emits 43.5 milliJoules of energy on each laser pulse, and has a total optical fiber area of 0.87 mm^2, the fluence is 43.5/0.87 = 50 mJ/mm^2.

Follow-up data were recorded during clinical visits at hospital discharge, and at 1-, 3- and 6-month intervals

Hz Hertz; a unit of frequency; pulses per second

Inclusion criteria

- ?? Signed informed consent obtained.
- ?? Symptomatic critical limb ischemia (Rutherford category 4, 5 or 6), stable for at least 2 weeks prior to study inclusion.
- ?? Lesions in the superficial femoral artery (SFA), popliteal, or infrapopliteal arteries
- ?? At least one angiographically identifiable infrageniculate (below-the-knee) artery
- ?? Patients must be poor surgical candidates, indicated by at least one of the following conditions:
  - ?? Absence of venous autologous grafts (that is, lack of a suitable vein to use for bypass)
  - ?? Poor (diffusely diseased or ? 1mm diameter) or no distal vessels available for graft anastamosis
  - ?? High risk of surgical mortality, evidenced by American Society of Anesthesiologists Physical Class 4 or higher

Infrapopliteal Peripheral arteries distal of the popliteal artery, including the tibio-peroneal trunk, peroneal, anterior tibial, dorsalis pedis (pedal), posterior tibial and distal posterior tibial (pedal) arteries.

LACI Laser Angioplasty for Critical Limb Ischemia

Laser burst software in the CVX-300 limits the laser operating duration to short bursts. The laser will fire at the repetition rate set by the user (between 25 and 40 pulses per second for peripheral atherectomy catheters) for five seconds or until the user releases the foot pedal, whichever comes sooner. Then the software enforces a mandatory 10-second wait period, after which the laser can fire another burst.

Limb salvage lack of major amputation, leaving the patient with an ambulatory foot. Limb salvage includes survival with minor amputation.

Major amputation amputation at or above the ankle. In practice, these are categorized into above-the-knee amputation (AKA) and below-the-knee amputation (BKA).

Minor amputation amputation at or distal to the mid-foot, leaving the patient with an ambulatory foot.

mJ milliJoule; 0.001 Joules; a unit of energy

Non-stented Legs subgroup of Registry Legs that were not stented in the index procedure

Peripheral Vascular Endpoint Alive with major amputation or critical limb ischemia at six months

Planned Amputation the expected and documented level of amputation required with or without a successful revascularization procedure

Primary Endpoint the primary endpoint of this study is limb salvage (absence of major amputation) at six months. Analysis of the primary endpoint was on a per-limb basis.

Procedure success (Angiographic) Procedural Success is defined as 50% or less residual stenosis on visual assessment of the planned area of treatment

PTA Percutaneous Transluminal (balloon) Angioplasty

Registry Group subgroup of All Patients, minus the Training Group. The Registry Group comprises the pivotal data from LACI Phase 2.

Registry Legs all Registry Group legs. Ten patients had two legs enrolled, so there are more observations in Registry Legs than there are patients in the Registry Group.

Repetition rate number of times per second that the excimer laser emits a pulse of light, usually expressed in Hz (pulses per second)

Rutherford Category

Category	Clinical Description	Objective Criteria
0	Asymptomatic : No hemodynamically significant occlusive disease	Normal treadmill /stress test
1	Mild Claudication	Completes treadmill exercise (>250m), Postexercise ankle pressure is >50 mm Hg, but >25 mm Hg less than normal
2	Moderate Claudication	Treadmill not completed (100-250 m)
3	Severe Claudication	Treadmill test failed (<100m) Post-exercise ankle pressure <50 mm Hg
4	Ischemic Rest Pain	Resting ankle pressure < 50-70 mm Hg, or plethysmographic, doppler or PPG waveforms demonstrating flat or barely pulsatile flow, or toe pressure < 30-50 mm Hg
5	Minor Tissue Loss Non-healing ulcer, focal gangrene with diffuse pedal ischemia	Same as 4

6	Major Tissue Loss Extending above transmetatarsal level - functional foot no longer salvageable.	Same as 4

Secondary Endpoints

1. "Peripheral vascular endpoint," which is major amputation or persistent CLI at 6 months (basis: limb)
2. Death during the follow-up period (basis: patient)
3. Incidence of minor amputation (basis: limb)
4. Persistent CLI (basis: limb)
5. Mean area percent healing of ulcers (basis: ulcer)
6. Surgical bypass in the leg (basis: limb)
7. Surgical bypass to a previously unavailable site (basis: limb)
8. Reduction in degree of planned lower extremity amputation (basis: limb)
9. Angiographic success rate (basis: limb)

Serious Adverse Event (SAE) an adverse event was defined as serious, if the event was fatal, life-threatening, disabling or resulted in prolongation of hospitalization. Therefore, the following were always serious adverse events:

Death
Myocardial Infarction
Cerebro-Vascular Incident (stroke)
Reintervention of treatment site during concurrent hospitalization
Major perforation, necessitating surgical repair
Acute Limb Ischemia necessitating intravascular intervention or thrombolytic drugs
Amputation due to distal thrombosis
Hematoma or false aneurysm necessitating surgical intervention
Nerve injury
Major amputation

Stented Legs subgroup of Registry Legs that were stented in the index procedure

Straight Line Flow unobstructed path of blood flow through the lower limb to the foot via a patent superficial femoral artery, patent popliteal artery and at least one patent infrapopliteal artery.

Training Group subgroup of All Patients consisting of the first 3 limbs treated at new LACI sites plus patients who were enrolled but did not meet the inclusion criteria.

Training Legs all legs in the Training Group. In this group, the number of legs equals the number of patients.

4. Introduction

Background

Peripheral arterial disease (PAD) afflicts approximately 25 million people in the United States over the age of 65 (1,2,3). Mild PAD manifests initially as intermittent claudication, in which a patient's walking distance is limited by the onset of leg pain, usually relieved by short periods of rest. Limb-threatening ischemia occurs when resting blood flow is insufficient to maintain metabolic requirements for non-exercising tissue. Symptoms of chronic limb ischemia (CLI) include rest pain, ulceration and gangrene. Unrelieved CLI will in most cases lead to amputation of some part of the lower limb. Up to 500,000 people suffer from CLI, with approximately 80,000 amputations performed in the US each year (1).

Surgical bypass is a common intervention for patients with CLI. Long-term results from autologous vein and in-situ vein bypass have been superior to polytetrafluorethylene or Dacron grafts (4-7), which show poor patency after a few months. Since the CLI patient presents with multiple profound comorbid conditions, the option of surgical intervention carries an unacceptable risk for a significant portion of the CLI population. Such patients typically present with advanced cardiac disease, renal dysfunction, or a lack of veins to be used for bypass grafting.

Catheter-based interventional techniques, such as percutaneous transluminal angioplasty (PTA) using balloons and stents, have shown promising results in several case series (8,9,21). In a series of 60 patients with successful PTA using balloon angioplasty alone (no stenting), 94% limb salvage was achieved at 1-year (21). The authors did not comment on how often PTA alone was not successful, or on the use and outcomes of other tandem modalities, such as thrombectomy, atherectomy, or stents. Two randomized trials comparing balloon angioplasty to surgery were reported, both in the mid-1980s before currently available anticoagulants and stents were available, and with very limited enrollment (8,12). In these and other studies, certain patterns of disease were identified that were not well suited to PTA (11,12): balloons have traditionally not done well in diffuse PAD, in which plaque remodeling tends to mitigate PTA effects fairly quickly. In cases where the disease extends throughout the legs, and many sites in the femoral-popliteal-tibial-pedal arch system are blocked, treatment at a few focal sites with PTA is insufficient to establish enough blood flow to help the patient. For this reason PTA is generally recommended only for focal disease shorter than 1 cm (15), which does not serve majority of the CLI population. Also, patients with severe systemic diseases, such as renal failure, have poor prognoses for healing anywhere in the body, including the legs.

This leaves a large segment of the CLI population – those who represent poor surgical candidates – without a clear treatment alternative. If the vascular disease pattern in these patients could be reduced to a simpler pattern, and if blood flow to the foot could be established for even a few months, symptoms would abate sufficiently to preclude amputation. This suggests that a suitable atherectomy procedure, such as excimer laser atherectomy (ELA), would benefit this patient group.

ELA actually removes (ablates; debulks) atheroma and thrombus. The excimer laser system uses a catheter packed with optical fibers to conduct pulses of ultraviolet light at 308 nm from a laser to a lesion in a patient's artery. The ultraviolet pulses ablate or debulk the lesion as the catheter tip is slowly advanced through the blockage. In a sense, the excimer catheter can "drill" through vascular blockages that prevent successful PTA. This gives ELA an advantage over PTA in its ability to traverse complex lesions and achieve technical success. The ability to remove atheroma transforms a long, complex lesion into a treated artery, perhaps with a single focal stenosis. Further, ELA has the beneficial effect on thrombus – seen in bench testing and in hundreds of peripheral ELA cases to date – of liquefying the thrombus, rather than breaking it into embolizing pieces. These technical features allow investigators to address arterial blockages that were formerly untreatable with percutaneous techniques.

Excimer laser coronary atherectomy (ELCA) has been commercially available in the US and Europe since 1993. Excimer laser atherectomy of the leg arteries has been practiced commercially in Europe since 1994.(13) In February 1999, FDA approved the Laser Angioplasty for Critical Ischemia (LACI) Phase 1 Registry. In this 25-limb study, excimer laser atherectomy was used to open arterial blockages near or below the knee in patients presenting with nonhealing ulcers or gangrene. The primary endpoint was healing at 3 months, defined by a ?50% reduction in the ulcer size as measured by photomorphography. Enrollment was completed in June 2000, with an ensuing 6-month follow-up period.

LACI Phase 1 showed that limb salvage at 6 months, without surgery, could be achieved in 70% of patients who presented with ulcers or gangrene and who were poor surgical candidates. Mortality and rates of minor amputation were nearly identical to established norms. (14-17) Of the 23 patients enrolled, four died from cardiac disease during the 6-month follow-up period and four had elective peripheral bypass. Four patients had planned minor amputation (toes and metatarsal only) with complete healing of the surgical site. These results strongly suggested that a high rate of limb salvage could be achieved without subjecting this population to surgery. (See the section "Additional Clinical Studies" in this report.)

Because the LACI Phase 1 outcomes revealed that excimer laser therapy was safe and feasible, and suggested that patient care could be improved by the therapy, a Phase 2 or pivotal trial was indicated. The LACI Phase 2 clinical study protocol evolved from the Phase 1 protocol, so that it harmonized with the recommendations of the TASC document (the current standard for definitions, endpoints, and treatment of PAD) (15), and FDA's various Draft Guidance documents.(18-20)

From a clinical perspective, ELA for CLI has multiple objectives. In descending order of urgency, these might include, among others:

- Removing an acute indication for primary amputation
- Limb salvage
- Healing the incision of a limited amputation
- Resolution of critical limb ischemia
- Providing a previously unavailable anastomosis site for surgical bypass
- Preservation of surgical options
- Providing temporary relief of rest pain

This consideration suggests that the primary endpoint of Phase 2 should be limb salvage. This agrees with FDA Guidance and the definitions in the TASC document. Further, the endpoint should be assessed at 6 months, instead of at the 3-months endpoint used in Phase 1. Secondary endpoints related to the objectives outlined above should also be tabulated.

Selection of a Control

Because ELA brings a new capability to peripheral atherectomy – ablating and removing arterial occlusions – the extent of disease present in the LACI population are not well treated by other interventional modalities. PTA does not offer an acceptable alternative for this patient group, because PTA is reserved for short, focal disease <1 cm in length (15) whereas the disease observed in LACI patients typically extends for at least 6 cm (see Appendix 2). Bypass surgery is also not recommended for the group of patients identified for LACI Phase 2. Study designs with a concurrent control group allocating patients to a single type of therapy cannot be recommended for the expected study population. Therefore a randomized study design, with a single well-defined therapy in the control group, cannot be ethically recommended for LACI Phase 2.

Fortunately the literature presents many case series of CLI patients. One of the largest, and most carefully conducted recent studies, was published in 1999:

> ICAI Study Group. Prostanoids for Chronic Critical Leg Ischemia: a randomized, controlled, open-label trial with Prostaglandin E1. Ann Intern Med 1999; 130:412-421

This paper, in a highly-respected, refereed journal, described a prospective, randomized drug study conducted in strict accordance with the TASC recommendations. The study included 1560 CLI patients, with 771 randomized to infusion of prostaglandin and 789 to no infusion, i.e. a variety of treatments selected on a patient-by-patient basis. These treatments included surgical intervention in 35%, intravascular intervention in 8%, and various medications in a majority of patients. Patient baseline characteristics, diagnostic variables, risk factors, in-hospital treatments, and outcome events at hospital discharge were tabulated for the treatment and control groups. Outcome events at 6 months were also tabulated for 661 prostanoid patients and 673 control patients; these included separate tabulations for death, amputation, persistent CLI, AMI-or-stroke, a "peripheral end point," and a "combined end point." Kaplan-Meier plots for three endpoints (death, amputation and persistence of critical leg ischemia) were also presented.

Because the LACI Phase 2 patients comprised poor surgical candidates, whereas the ICAI study included all CLI patients, the ICAI study control population was not strictly equivalent to LACI across all patient characteristics. Because of their poor surgical candidacy, LACI population was expected to have more comorbidity than the ICAI study patients. One might expect these comorbidities to bias the LACI results to worse outcomes, and in this sense the ICAI data represents a conservative baseline from which to compare LACI results.

Selection of Primary and Secondary Endpoints

In accordance with the TASC document, the primary endpoint was limb salvage. This endpoint is represented by the amputation endpoint of the ICAI study. It should be noted that CLI patients typically present with profound comorbid (vascular and other) conditions, as evidenced by the 14% mortality at 6 months in the ICAI control group. The "peripheral endpoint" and the "combined end point" of the ICAI study (which is harmonized to Recommendation 105 if the TASC document) are too sensitive to comorbid disease (such as illiac occlusive disease, coronary disease, diabetes, etc.) to give unconfounded statistical evidence of the clinical usefulness of the LACI intervention. Therefore the "peripheral endpoint" and "combined endpoint" at 6-months were secondary endpoints for LACI Phase 2.

Since no endpoint is associated with measures of vessel patency, no angiographic core lab was employed in LACI. However, a photo-morphography core lab was used to assess wound area for all patients, so that an unbiased quantitative measure of wound healing could be made.

5. Detailed Summary

Study Design

LACI Phase 2 was a prospective consecutive multicenter clinical registry carried out in the United States and Europe. A historical benchmark conforming to recently published standards was used. Patients were eligible for study inclusion if there was objective evidence of chronic critical limb ischemia (rest pain or non-healing ulcerative lesions or gangrene) with lesions in the SFA, popliteal and/or infrapopliteal arteries. At 12 US sites and 3 German sites, 160 patients with 170 ischemic limbs (the All Patients Group) were enrolled during the period of April 2001 through April 2002. Enrollment at each site was begun after completion of several tasks including: Institutional Review Board (or Ethics Committee) approval, signing of institutional agreement, investigator agreement and financial disclosure, study initiation visit by the study monitor, and shipment of necessary forms and equipment.

The purpose of this study was to provide valid scientific evidence of the safety and efficacy of excimer laser atherectomy, with or without adjunct PTA, for the revascularization of occluded or partially occluded target lesions in the infrainguinal arteries responsible for critical limb ischemia (CLI).

The primary objective of the study is to determine whether excimer laser ablation of target vascular obstructions, with or without adjunctive balloon angioplasty, can prevent amputations above the ankle and relieve CLI.

Inclusion and Exclusion Criteria

Inclusion Criteria:

- ?? Signed informed consent obtained.
- ?? Symptomatic critical limb ischemia (Rutherford category 4, 5 or 6), stable for at least 2 weeks prior to study inclusion.

- ?? Lesions in the superficial femoral artery (SFA), popliteal, or infrapopliteal arteries
- ?? At least one angiographically identifiable infrageniculate (below-the-knee) artery
- ?? Patients must be poor surgical candidates, indicated by at least one of the following conditions:
  - ?? Absence of venous autologous grafts (that is, lack of a suitable vein to use for bypass)
  - ?? Poor (diffusely diseased or ? 1mm diameter) or no distal vessels available for graft anastamosis
  - ?? High risk of surgical mortality, evidenced by American Society of Anesthesiologists Physical Class 4 or higher

Exclusion Criteria:

- ?? Age below 18 years
- ?? Pregnancy, or plan to become pregnant
- ?? Participation in another cardiovascular or peripheral vascular IDE study.
- ?? Myocardial infarction (MI) in prior month
- ?? Stents at treatment site
- ?? Disorders or allergies precluding use of radiographic contrast
- ?? Renal insufficiency severe enough to contraindicate use of radiographic contrast
- ?? Contraindication to treatment with anticoagulants
- ?? Untreated ipsilateral iliac stenosis >70%
- ?? Inability or unwillingness of the patient to comply with intended examinations.
- ?? Unavailability of required procedural or imaging equipment
- ?? Lesion located in a graft
- ?? Hemodynamically significant arrhythmia or left ventricular ejection fraction <20%
- ?? Life expectancy less than 6 months
- ?? Necrosis necessitating major amputation

Endpoints

Primary endpoint

The primary endpoint of this study is limb salvage (absence of major amputation) at six (6) months. Analysis of the primary endpoint was on a per-limb basis.

Secondary endpoints

1. "Peripheral vascular endpoint," which is major amputation or persistent CLI at 6 months (basis: limb)
2. Death during the follow-up period (basis: patient)
3. Incidence of minor amputation (basis: limb)
4. Persistent CLI (basis: limb)
5. Mean area percent healing of ulcers (basis: ulcer)
6. Surgical bypass in the leg (basis: limb)
7. Surgical bypass to a previously unavailable site (basis: limb)

8. Reduction in degree of planned lower extremity amputation (basis: limb)
9. Angiographic success rate (basis: limb)
   Angiographic Procedural Success is defined as 50% or less residual stenosis on visual assessment of the planned area of treatment after completion of treatment

Safety Endpoints: Serious Adverse Events

The main safety endpoint in this study was death during the 6-month follow-up period. In addition, incidence of other adverse events was captured. An adverse event was defined as serious, if the event was fatal, life-threatening, disabling or resulted in prolongation of hospitalization. Therefore, the following were always serious adverse events:

Death
Myocardial Infarction
Cerebro-Vascular Incident (stroke)
Reintervention of treatment site during concurrent hospitalization
Major perforation, necessitating surgical repair
Acute Limb Ischemia necessitating intravascular intervention or thrombolytic drugs
Amputation due to distal thrombosis
Hematoma or false aneurysm necessitating surgical intervention
Nerve injury
Major amputation

These serious adverse events are defined/described as follows:

1) Death:

All deaths were recorded and were considered to be procedurally related unless they are documented to the contrary.

2) Myocardial Infarction

A myocardial infarction was diagnosed based on 2 of the following 3 conditions: clinical symptoms, EKG changes, and increases in cardiac enzymes. Clinical criteria included signs and / or symptoms (such as chest pain lasting longer than 20-30 minutes, flash pulmonary edema, etc.) consistent with an acute myocardial infarction. EKG changes included a new left bundle branch block or new significant Q waves in at least 2 contiguous leads (greater than or equal to 0.04 sec). Enzyme criteria included (in order of priority) elevation of CK-MB to > 2X upper limit of reference range; elevation of troponin I or T to > 2X the upper limit of the reference range, if CK-MB was not available; or total CK > 2X upper limit of reference range, if CK-MB and troponins were not available.

3) Cerebral Vascular Incident:

A cerebral vascular incident (CVI or Stroke) was a vascular or systemically induced injury to the brain usually resulting in necrosis of tissue and impairment of function. A CVI can be caused by vasospasm, embolization, atherosclerosis, aneurysm rupture with hemorrhage, hypertension, hypovolemia, vascular exsaguination due to blood-thinning or antiplatelet therapy, as well as

extrinsic trauma. A CVI is characterized by, but not exclusively, the following clinical manifestations; electroencephalographic (EEG) abnormalities, mild to major mental confusion and deficits of cognitive ability, slurred speech or aphasia, visual deficits, focal or generalized loss of balance and coordination, vasotone responses, focal or generalized neuromotor deficits, muscular tremor or spasm, paralysis or death. A CVI is sometimes transient (TIA – transient ischemic attack) lasting minutes to hours without permanent disability or severe (instantaneous or gradual progression of symptoms) with permanent disability. The extent of injury is based on the location and amount of tissue effected, time to treatment, age and other pre-existing conditions.

4) Re-intervention of treatment site:

A repeat angioplasty or surgical intervention was defined as the return of the patient to the catheterization laboratory for re-insertion of a sheath followed by a new angioplasty or attempt at the same site during the concurrent hospitalization. Re-intervention during follow-up was autoadjudicated as an SAE by the Data Safety Monitoring Committee.

It was advised that elective repeat angioplasty or any surgical intervention at the treatment site during follow-up should be preceded by a Doppler Ultrasound ABI showing objective evidence of ischemia. In addition, visual inspection by angiography of the treated artery should indicate a diameter of stenosis greater than 50%.

5) Major perforation, necessitating surgical repair:

Should a perforation (leakage of free contrast into the area around the vessel documented by angiography), which cannot be sealed with additional balloon inflations, occur, surgical repair should be considered to avoid unnecessary prolonged hospitalization. Surgical repair was defined as any surgical intervention to seal the perforation and stop the bleeding or clean the Hematoma.

6) Acute Limb Ischemia:

Acute Limb Ischemia was defined as any form of ischemia that requires immediate therapy whether this is with thrombolysis or any reintervention (PTA or surgery). Acute Limb Ischemia was typically caused by re-occlusion of the treatment site (thrombus, dissection, acute recoil) or by distal embolization.

7) Amputation due to distal embolization:

Unplanned amputation (minor or major) secondary to distal embolization occurring during the index procedure was classified as a serious adverse event.

8) Hematoma or false aneurysm necessitating surgical intervention:

The procedure and the related anticoagulation infrequently led to bleeding at the puncture site requiring surgical intervention. A large hematoma or false aneurysm necessitating a surgical

intervention may also require surgical care. The incidence of surgical care for these conditions was classified as a serious adverse event.

9) Nerve Injury

Mechanical injury of the femoral nerve caused by the insertion sheath is extremely rare. Nerve injuries caused by large hematoma or false aneurysm occur in less than 1 of 1,000 patients. In the majority of the cases a surgical intervention is not necessary. (This type of event was not observed in LACI Phase 2).

10) Major amputation

Major amputation is excision of the lower limb at or above the ankle. In practice, below-the-knee amputation (BKA) and above-the-knee amputation (AKA) were observed.

Minor amputation, which is amputation at or below the mid-foot, was an adverse event (which it was hoped the LACI procedure can preclude). However, for the purposes of event categorization, minor amputation was not a serious adverse event. This harmonizes with Recommendation 81 of the TASC document, which suggests that limb salvage is successful when the patient retains a functional foot.

For some enrolled patients it is inevitable that they will need minor amputation, wound debridement, skin graft or wound care treatment. Therefore, the protocol and case report form were designed to document such treatment that was expected prior to intervention. Any treatment documented in this way, regardless of whether the patient requires rehospitalization for the procedure, was not an SAE.

In addition, many LACI patients had comorbidities that required some form of regular care, such as dialysis for renal patients, blood transfusions for anemic patients and other conditions that had previously been part of the patients' medical history. Therefore, if a patient enrolled in the LACI study required care that reflected their previous medical history or was planned prior to their enrollment in the study, regardless of the requirement for rehospitalization, it was not an SAE. However, the incidence of such events was captured on the appropriate Follow-up CRF.

Safety Endpoints: Procedural Complications

The following treatment modalities after the occurrence of complications were recommended:

Spasm: Nitroglycerin, according to local institutional protocols.
Additional balloon inflations

Thrombus: Additional heparin, prolonged heparin infusion or thrombolysis.

Flow-limiting dissections or threatened closure: Additional prolonged balloon inflations, prolonged anticoagulant infusion or stenting

Acute recoil: Moderate: - Additional balloon inflations at higher pressure or larger balloon.

Severe: - Stent implantation

Perforation: Moderate: - Seal with prolonged balloon inflations

Severe: - Give anticoagulant antagonist
- Seal with prolonged balloon inflations
- Surgical repair

Interventional Procedure

The patient was prepared and draped for an interventional intravascular procedure delivered via the common femoral artery. Typically this involved a Seldinger approach, with the use of a contralateral guide catheter to navigate across the iliac bifurcation. Alternatively, an ipsilateral antegrade puncture was used with an appropriate, shorter introducer. Diagnostic angiography provided a "roadmap" of infrainguinal arteries and the lesions therein.

Prior to therapy, a guidewire must cross the entire occlusion and be in the distal vessel beyond the target lesion. Only approved conventional mechanical guidewires were permitted during the procedure. If free movement of the wire tip within the distal vessel was not observed, the guidewire was withdrawn and redirected. To ensure intra-luminal position of the guidewire, a low profile infusion catheter may be advanced over the guide wire distal to the target lesion. Distal run-off was determined by angiographic visualization during contrast injection. As an alternate method of recanalization, laser ablation could be used in a step-by-step manner where the guidewire and then a laser catheter are sequentially advanced and activated (mm by mm) until the occlusion or stenosis was crossed.

After the wire crossed the target lesion, the occlusion or stenosis was treated with excimer laser atherectomy, unless satisfactory debulking had already been achieved through use of the step by step approach. Use of all laser catheter sizes was allowed. It was recommended to ablate as much tissue as possible in order to achieve an optimal laser channel (at least 30-50% of vessel diameter).

The maximum laser catheter size was selected according to the minimum vessel reference diameter intended for treatment, and by following the specific laser catheter instructions for use. In brief, the maximum laser catheter size followed a guideline:

Minimum reference vessel diameter	Laser catheter diameter
1.5 mm	0.9 mm
2.0 mm	1.4 mm
2.3 mm	1.7 mm
2.6 mm	2.0 mm
2.9 mm	2.2 mm
3.1 mm	2.5 mm

To debulk a lesion, the laser catheter tip must be in contact with tissue. The ablation depth per pulse is approximately 0.05 mm. To maximize ablation versus dottering (pushing tissue), the laser catheter should be advanced at a speed of approximately 0.5-1 mm/sec while the laser is activated. During laser ablation, saline infusion should be infused. After the laser catheter crossed an occlusion an angiogram was typically made to assess the vessel lumen. Additional passes were made to improve the initial laser result at the discretion of the investigator. In general, not more than two passes were made with the same catheter size.

Fluence (mJ/mm^2) and repetition rate (pulses per second) were adjusted according to lesion morphology (e.g. soft or hard tissue). When fluence is increased, the potential to ablate tissue with a higher density is increased. When the repetition rate is increased, the ablation rate is increased. The following recommendations were made for laser parameter settings:

Table 2 Recommended laser parameters

Lesion morphology	fluence [mJ/mm2]	repetition rate [pulses/second]
de novo lesions	50	25
when resistance is encountered	60	25
if resistance is still encountered	60	40
when crossed, for additional passes, go back to	50	25
calcified lesions	60	25
when resistance is encountered	60	30
if resistance is still encountered	60	40
when crossed, for additional passes, go back to	50	25

Blood as well as radiographic contrast highly absorb ultraviolet laser light. Saline, on the other hand, transmits ultraviolet light, resulting in greater transmission of the laser light to the lesion. Therefore, saline infusion was recommended whenever the laser system was activated within the vessel.

Since laser catheters were not larger than 2.5 mm in diameter, balloon dilatations were required to optimize the angiographic result. Therefore, adjunctive balloon angioplasty was expected in the majority of cases.

The balloon catheters were be sized according to the intended vessel diameter (1.5-5 mm). As indicated by lesion morphology, overlapping inflations were performed according to the specific manufacturer instructions for use. Although discouraged, the use of approved intra-vascular endoprostheses (stents) according to the specific manufacturer instructions for use was allowed in case of acute recoil, flow-limiting dissection, or threatened closure. During balloon inflations it was recommended that the distal vessel be flushed with a saline/heparin solution through the balloon catheters' inner lumen in order to avoid distal embolization and/or local thrombosis. If distal micro-embolization or thrombus was seen or suspected, local thrombolysis could be

administered. If remaining thrombotic material was seen or suspected within the treated occlusion, local thrombolysis could be applied.

Concomitant Medication during hospital stay and follow-up

* Anticoagulants: According to institutional protocol.
Although the LACI Protocol did not specify what pharmacological agents should be given, it was recommended that all patients should receive pharmacologics according to local institutional protocols. However, listed below were some recommendations.

Table 3 Recommended anticoagulation

Pre-Procedure	**Procedure**	**Post Procedure**	
At least 24hrs:		*Option 1*	*Option 2*
ASA	ASA	ASA	LMWH X 2wks.
+/- Plavix (must be on Plavix if ASA allergic)	+/- Plavix	Plavix X 30d.	ASA
	Heparin		Coumadin to INR 3.0 – 4.0

* Thrombolytics: In cases of possible thrombosis a thrombolytic and/or antiplatelet therapy could be used in conjunction with the intervention, according to institutional protocols.

During the study, investigators recorded pre-admission medications by checking yes/no boxes on the LACI Phase 2 case report form. Ten (10) categories of therapeutic agents, commonly used in the treatment of CLI patients, were queried. The number of patients treated with each of the ten types of agents are tabulated below, with percentages calculated on a per patient basis (N=145 patients). Over half (61%) of the cases were being treated using antiplatelet therapy, and no patients were receiving thrombolytics at the time of admission. Additionally, pre-enrollment data show 108 patients being treated for hypertension.

Table 4 – Number of Patients receiving Pre-admission medications, in Ten (10) Categorical Types

TYPE OF PRE-ADMISSION MEDICATION	NUMBER OF PATIENTS TREATED WITH MEDICATION	
	Frequency of Patients	Percentage of 145 Patients
Antiplatelet	88	61%
Anticoagulant	37	26%
Analgesic	54	37%
Vasoactive	15	10%
Heparin	14	10%
Calcium Antagonist	38	26%
Beta Blocker	54	37%
Nitrates	22	15%
ACE Inhibitor	54	37%
Thrombolytic	0	0%

Many patients were receiving more than one type of medication, but some (7/145=5%) were not taking any of the ten types of drugs tabulated above. No patients were taking more than 6 types of drugs

Table 5 – Number of Patients receiving Follow-up Medications, in Six (6) Categorical Types

TYPE OF FOLLOW-UP MEDICATION	NUMBER OF PATIENTS TREATED WITH MEDICATION	
	Frequency of Patients	Percentage of 145 Patients
Antiplatelet	122	84%
Anticoagulant	50	34%
Analgesic	65	45%
Vasoactive	29	20%
Heparin	11	8%
Thrombolytic	0	0%

.

Data Collection

Data were collected by research coordinators at each institution and entered on reprinted 2 part NCR (non-carbon) paper forms. During a visit to a site, a study monitor compared the data on the forms to hospital records before taking the forms from the institution. In the US, Spectranetics personnel performed the monitor duties. In Germany, a contract monitor was provided by CorTrial, a contract research organization. Completed and monitored report forms were then forwarded to the data coordination center (DCC) at Spectranetics. All forms were monitored before reaching the DCC.

At the DCC, data were keyed into an electronic database (SAS/Stat, SAS Institute, Cary, NC). Thereafter data quality and integrity checks were performed according to standard protocols; in

practice, 100% of the data were actually checked against the paper forms. During key-in, data checking and data analysis, edit queries were generated for missing data or out-of-range items. Edit queries were closed by receiving clarification from study site research coordinators and editing the electronic database accordingly.

Digital images of patients' limbs were recorded and handled as described in the section on digital morphography.

Digital Morphography

Digital photography (morphography) was performed at inclusion prior to treatment to document and map the extent of lower limb or pedal ulceration(s) for all patients. Repeat morphography was done at the 3- and 6-month follow-up visit using the same photographic projections obtained at inclusion. A digital camera (Kodak DC260 or DC 290) was used to photograph the subject. Each subject was photographed from five standard photo angles: three angles of the lower leg and the top (dorsal) and the bottom (plantar) surfaces of the foot. The lower leg images were taken while the patient was in a supine position by photographing the anterior- medial and anterior- lateral aspect of the leg with the patient lying on his (her) back and photographing the posterior aspect of the leg while the patient was positioned on his (her) side (the side opposite of the leg to be photographed) or by having the patient hang his (her) leg over the side of the bed, or while the patient was seated in a chair.

Additional photos were taken of ulcers if they; 1) appeared on the tips of the toes, one photo was taken from directly in front of the tips of the toes, or 2) on the edge of the foot near the fifth metatarsal bone, one photo was from an angle 60? from the vertical aimed at the fifth metatarsal, or 3) are small and are located on the lower leg, a photo was taken of each small ulcer, with the camera angle coincident with the normal to the center of the ulcer. A reasonable definition of "small ulcer" was ulcer that can be captured entirely in the view finder of the digital camera. Any lesion that wrapped partially or entirely around the leg should be captured by taking three close-up images of the ulcer at 120? apart.

A 3x3 cm calibration target was typically visible in all photos. The calibration target was placed in the plane of the ulcer so that the centroid of the calibration target was coincident with the camera angle.

Photos were stored in flash memory cards by the camera. The memory cards were mailed to the core lab for analysis. The core lab estimated the actual area of the ulcer from the photos, using the calibration target as a calibration. For large ulcers on the lower leg, the true area was estimated by adding the image areas observed in the three 120? photo angles. For small ulcers on the lower leg, or on the toes or edge of the foot, the additional photos were used. In the case of an ulcer wrapped around the fifth metatarsal, ulcer areas from two images of the foot, taken 120° apart, were combined.

Statistical Analysis

Hypotheses and Sample Size Calculation

The results of LACI Phase 1 suggested that limb salvage can be expected in 86% of patients reaching the 6-month follow-up(= $?_2$). This is very close to the 86.8% figure observed in the ICAI control group (= $?_1$). LACI Phase 2 was intended to show results that are at least as good as the ICAI control group. That is, the hypotheses would be

$H_0 : ?_1 \; ? \; ?_2$
$H_1 : ?_1 > ?_2$

Enrollment should be large enough to have sufficient statistical power to reject H_0 if $? = | ?_1 - ?_2|$ > 10%. This difference of ten percentage points (between the ICAI benchmark and the threshold for rejecting H_0) was chosen by the Steering Committee on the basis of historical expectations for poor surgical candidates (3,9,12). Using the methods of Lachin (Lachin JM. Introduction to sample size determination and power analysis for clinical trials. Control Clin Trials 1981; 2:100) we set

$? = .05$	1-sided $z_?$	$= 1.645$
$1 - ? = .80$		$z_{1-?} = .842$
$p_0 = .768$	$p_1 = .868$	

and calculate that N = 96 patients should be enrolled.

These calculations can be checked by using the equations of section 3.4 of Fleiss (Fleiss JL. Statistical Methods for Rates and Proportions, 2nd ed. John Wiley & Sons, New York, ©1981), which are applicable to studies with unequal sample sizes. In this case, we set:

$? = .05$	2-sided $c(? /2)$	$= 1.645$
$1 - ? = .80$		$c(1-?) = -.842$
P1 = .868	observed proportion from the control group	
P2 = .768	expected proportion from the test group	
r = .2008		

The equations render:

m = 577	the observed number of patients in the control group reaching 6-months
rm = 116	the required number of observations in the test group.

This calculation suggests that enrollment should be approximatley 116 observations, which is a slightly higher number than calculated from Lachin's formulas. To be conservative, and to ensure a marginally higher statistical power than the minimum required by Lachin, LACI Phase 2 planned for an enrollment of 116 patients.

As a second check of the calculations, we use the methods of Fleiss to calculate the interval around the benchmark value of .868 that would fail the Z-test. If the LACI Phase 2 results fall

above .811 with n = 116 observations, the calculated z would be greater than -1.645, indicating that H_0 should not be rejected.

A study size of 116 patients gives enough power to establish a statistically significant difference between the ICAI control and LACI Phase 2 if the latter fall outside the following intervals for two safety endpoints (using a Z-test with $z_{crit} = 1.645$):

	ICAI control	Interval of equivalence for LACI Phase 2
Death (all causes)	96/673 (14.3%)	8.5% - 20.1%
Nonfatal MI-or-stroke	4/673 (0.6%)	0% - 2.2%

Allowance was made for patient deaths and dropouts. The ICAI study observed 14% deaths at six months. This implies that LACI Phase 2 enrollment should be increased by 15 patients, so that statistical power can be preserved. As LACI Phase 1 demonstrated, a 5% withdrawal at the 6-month endpoint was expected. This implies that enrollment should be increased by (another) 5 patients. The total registry enrollment would then be 116 + 15 + 5 = 137 patients. These patients will constitute the "data pool."

In addition, it was estimated that up to half of the investigators will not have prior experience with infrainguinal excimer laser angioplasty; the other half of the investigators will have previous experience with the technology. The protocol allows for these investigators to treat up to three patients as part of their training. These patients will be pooled as “training cases“ and may amount to as many as (20/2) * 3 = 30 patients. The total number of patients treated during the LACI Phase 2 study would then be 137 + 30 = 167.

Statistical Analyses Performed

Data were analyzed using the programmable features of the SAS database system to create tables of frequencies, means, standard deviations and ranges. An "intent-to-treat" method was used for analyzing the Registry Group, that is, the basis for all frequency calculations was the number of patients enrolled or the number of limbs enrolled. The basis for all Control Group calculations is the number of patients. The Control Group publication reported serious adverse events on the basis of the 789 patients intially enrolled, but the 6-month primary endpoints were reported for a 673-patient subgroup (116 patients were withdrawn from the 6-month analysis because they were enrolled at sites with unreliable data).

Comparisons between the Registry Group and the Control Group were made by loading data into a spreadsheet, and calculating differences and 95% confidence intervals. For some comparisons, p-values were calculated from 2-sided continuity-corrected Chi-square, unless a cell count was ? 5, in which case Fisher's Exact was used. A univariable Cox proportional hazards model for 6month death and major amputation is fitted by using these variables respectively: age, gender, height, weight, leg of Rutherford classification 6, weeks of documented critical limb ischemia, previous ulceration/gangrene, previous CAD, previous CVA, previous hypertension, previous diabetes, previous pain (in treatment limb), previous minor amputation. Among the 26 models it

was found that age was a significant predictor for 6 month death, and leg of Rutherford classification 6 was significant for 6 month major amputation. Since there was no evidence that any factor would add significantly to the one factor in each model, multiple analyses were not explored.

Historical Control

The LACI control was the Control Group in the randomized trial reported in:

> ICAI Study Group. Prostanoids for Chronic Critical Leg Ischemia: a randomized, controlled, open-label trial with Prostaglandin E1. Ann Intern Med 1999; 130:412-421

A copy of this article appears in Appendix 1.

Patient Group Definitions

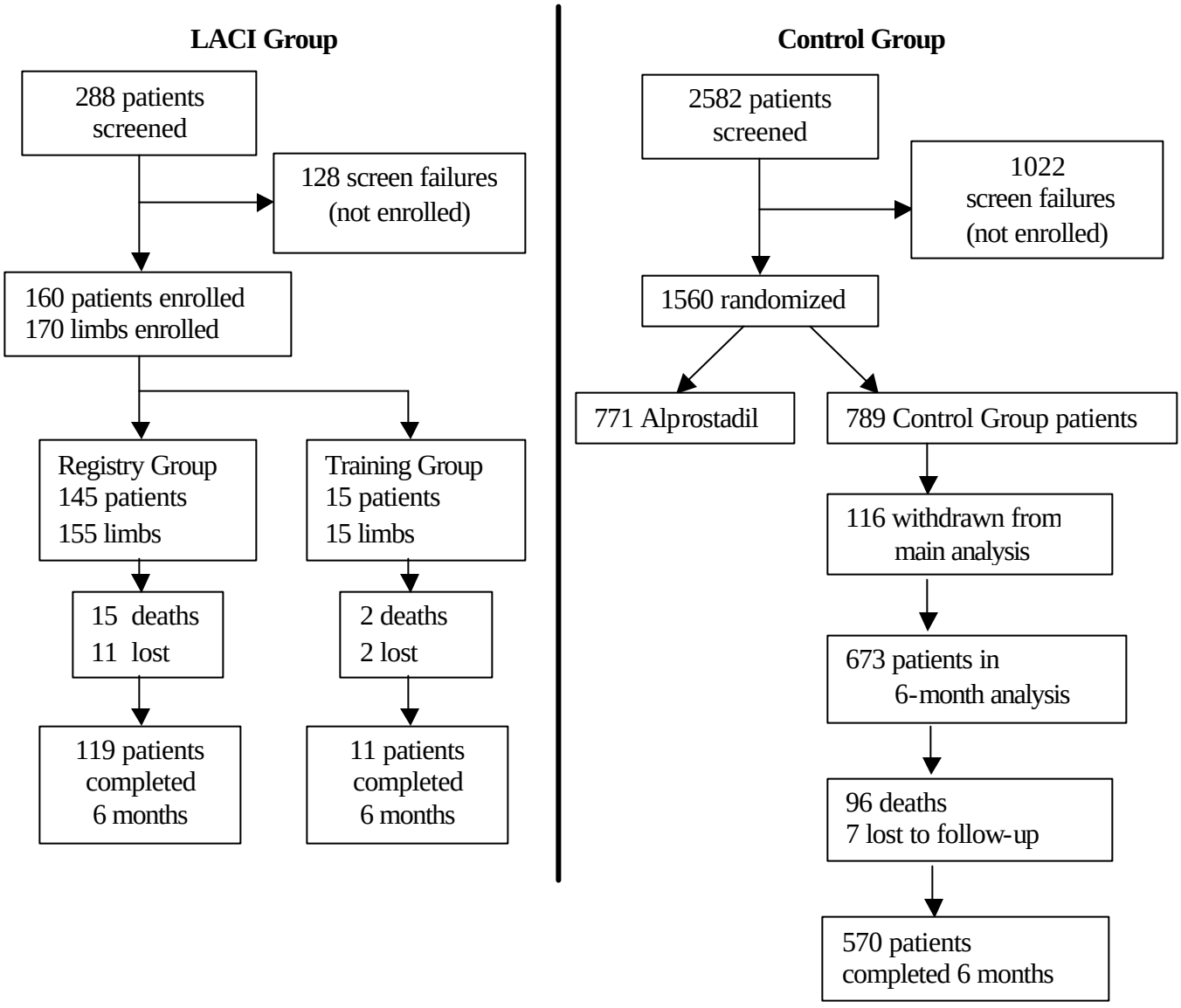
All Patients	all patients enrolled in LACI Phase 2
Training Group	subgroup of All Patients consisting of first 3 patients treated at new LACI sites plus patients who were enrolled but did not meet the inclusion criteria for Rutherford Category. This group has no patients in common with the Registry Group.
Training Legs	all legs in the Training Group. In this group, the number of legs equals the number of patients.
Registry Group	subgroup of All Patients, minus the Training Group. The Registry Group comprises the pivotal data from LACI Phase 2.
Registry Legs	all Registry Group legs. Ten patients had two legs enrolled, so there are more observations in Registry Legs than there are patients in the Registry Group.
Stented Legs	subgroup of Registry Legs that were stented in the index procedure
Nonstented Legs	subgroup of Registry Legs that were not stented in the index procedure
Category 4 Legs	subgroup of Registry Legs that presented with rest pain only (that is, Rutherford Category 4)
Category 5-6 Legs	subgroup of Registry Legs that presented with ulcerations and/or gangrene, or minor amputation required (that is, Rutherford Category 5 or 6)
Control Group	the Control Group patients in the randomized trial reported in: ICAI Study Group. Prostanoids for Chronic Critical Leg Ischemia: a randomized, controlled, open-label trial with Prostaglandin E1. Ann Intern Med 1999; 130:412-421

Patient Enrollment

At 15 sites (12 in the USA, 3 in Germany), patients presenting for intravascular treatment of CLI were screened during the period of April 2001 - April 2002. Patients who met all study criteria, and who signed an informed consent document, were enrolled. Four sites had not previously participated in LACI Phase 1 or the PELA Trial (Peripheral Excimer Laser Atherectomy), which studied the use of peripheral laser catheters on claudicants; these sites were allowed up to 3 roll-in patients per site. Data on roll-in patients were pooled in the Training Group. Data intended for comparison with the Control Group were pooled in the Registry Group. The union of the Registry Group and the Training Group represents all patients enrolled in LACI Phase 2.

After treatment it was retrospectively found that 5 patients did not meet inclusion criteria (they were Rutherford Category 3, claudicants without rest pain or ulcers). Nevertheless, full data on these patients were collected and, on the advice of the Steering Committee, pooled with the Training Group. Patient flow is shown in Figure 1.

Figure 1. Patient flow in LACI Phase 2 Group and Control Group



Initial enrollment was relatively slow, until December 2001, when several sites with high patient volume were activated. Thereafter enrollment averaged about 25 patients per month. At the conclusion of enrollment, 35% of sites had enrolled 68% of patients.

Follow-up

Follow-up consisted of data collection at hospital discharge, and clinical visits at 1-, 3- and 6-month intervals. At each stage of follow-up, a portion of the case report form was completed by the site research coordinator. Follow-up forms were monitored and collected as they became available; all follow-up was collected by the end of December 2002.

If an event occurred that may be a Serious Adverse Event (SAE), a SAE Report form was completed and immediately FAXed to the data coordination center and keyed into the database. Following receipt of the SAE form and any supporting documents, the SAE was adjudicated, and the adjudication results also keyed into the database.

Table 6 Assessments performed at each interval.

Visits	0 Screening	1 Inclusion/ Treatment	2 Discharge	3 1 month follow-up	4 3 month follow-up	5 6 month follow-up
Medical History	x					
Medication	x			x	x	x
Physical Exam		x	x	x	x	x
ABI		x	x	x	x	x
Clinical category of chronic limb ischemia	x		x	x	x	x
Angiography	x	x				
Digital Morphography		x			x	x
Study inclusion		x				
Blood samples		x				
Angioplasty		x				
Clinical events		x	x	x	x	x

Committees

Steering Committee

The Steering Committee decided on matters concerning the management of the study, such as reactions to protocol violations, amendments of the protocol, reaction to safety reports and publication of the study results.

The members of the Steering Committee were:

John Laird, MD	Washington Hospital Center, Washington, D.C. (Principal Investigator)
Bruce Gray DO	Greenville Memorial Hospital, Greenville, SC (Investigator)
W. Grundfest, MD	Cedars Sinai Medical Center, Los Angeles, CA (Medical Consultant)
Chris Reiser, Ph.D.	Spectranetics Corporation, Colorado Springs, CO (non-voting sponsor Representative)

Data Safety Monitoring Committee (DSMC)

The DSMC will reviewed the preliminary analysis of adverse events and the primary endpoint. Periodic reports from the Data Coordinating Center were provided to the Safety Committee on request. The DSMC also reviewed the final analysis. DSMC meetings were held on 7/10/02 and 1/10/03. The DSMC chairman was briefed on a more frequent basis by e-mail.

The members of the DSMC, including a biostatistician, were independent persons not involved in any other matters of this trial. The members included:

Mark Burket MD	Medical College of Ohio, Toledo, OH (Chairman)
Sadik Khuder PhD	Medical College of Ohio, Toledo, OH (statistician)
Charles Byrd MD	Broward General Medical Center, Ft Lauderdale, FL

Critical Event Committee

A member of the Critical Event Committee reviewed all adverse events reported during the study, and classified them according to the definitions in the protocol.

CEC members could be physicians familiar with peripheral interventional techniques and excimer laser atherectomy. CEC members were independent persons not involved in any other matters of this trial. They were not LACI investigators, members of a LACI Committee, or a coworker of a LACI investigator. They did not own sponsor stock.

CEC members could be fellows or physicians-in-residency. CEC members received honoraria for participation in meetings and reimbursement for expenses.

During the course of the study, it was found that one CEC member was sufficient to perform all duties related to the study. Hence the CEC committee consisted of:

Bhagat Reddy MD	Vanderbilt University, Nashville, TN (CEC member)

The CEC adjudicated SAE reports on 5/18/02, 9/14/02, 11/8/02, 12/1/02, and 1/3/03.

6. Results

Within All Patients, 52 patients (58 limbs) were enrolled in Germany, and 108 patients (112 limbs) were enrolled in the USA. The top 4 sites enrolled 58% of patients.

Table 7 Enrollment, All Patients

Group	Investigator	Site Code	Site Name	Patients	Legs
Registry	Mitar Vranic	AHI	Arizona Heart Institute	23	25
	Frank Bunch	CAR	Springhill Memorial	5	5
	Thomas Vogl / Joern Balzer	FRA	Univ. Frankfurt	6	6
	Dan Garnic	GLE	Glendale Memorial Hospital	7	8
	Bruce Gray	GRE	Greenville Hospital	19	19
	John Shuck	LAN	Lankenau	8	8
	Giancarlo Biamino / Dierk Scheinert	LEI	Hertzentrum Leipzig	24	28
	Gino Sedillo	MAN	Manatee Hospital	10	11
	Tyrone Collins	OCH	Ochsner Clinic	1	1
	Gary Ansel	RIV	Riverside Memorial Hosp.	7	7
	David Cohen	SJO	St. Joseph's (Paterson, NJ)	7	7
	Mark Mewissen	SLM	St. Lukes (Milwaukee)	1	1
	John Laird	WHC	Washington Hospital Center	5	5
	Thomas Zeller	ZEL	Hertzentrum Bad Krozingen	22	24
			subtotal:	145	155
Training	Mitar Vranic	AHI	Arizona Heart Institute	4	4
	Gino Sedillo	MAN	Manatee Hospital	4	4
	Frederick Beavers	NYH	New York Presbyterian	1	1
	David Cohen	SJO	St. Joseph's (Paterson)	3	3
	Mark Mewissen	SLM	St. Lukes (Milwaukee)	3	3
			subtotal:	15	15
			total:	160	170

NOTES:
1. Manatee Hospital enrolled one patient as both a Training leg (MAN T03) and a Registry leg (MAN 004).
2. A full listing of investigators and sites may be found in Appendix 3

Table 8 Baseline patient characteristics, Registry Group vs. Control Group; Training Group

	Registry Group n= 145		Control Group n=789				Training Group n=15	
					Difference	**95% CI in Difference**		
Age	72 ? 10 (45 - 91)		71 ? 10		1	-0.8 to 2.8	73 ? 12 (52 – 91)	
	n	**%**	**n**	**%**	**Difference**	**95% CI in Difference**	**n**	**%**
Gender:								
Male	77	53%	572	72%	-19.4%	-28.5% to –10.3%	6	40%
Previous Cardiovascular Illness:								
Stroke (CVA)	30	21%	92	12%	9.0%	1.7% to 16.4%	2	13%
Myocardial Infarction (MI)	33	23%	120	15.%	7.5%	1.9% TO 16.1%	2	13%
Coronary Artery Disease (CAD)	72	50%	DNA				7	47%
Previous Surgical Interventions:								
Coronary Artery Bypass (CABG)	24	17%	DNA				4	27%
Coronary Angioplasty (PCTA)	21	14%	DNA				2	13%
Risk Factors Present at Enrollment:								
Diabetes	95	66%	309	39%	26.4%	17.5% to 35.2%	7	47%
Hypertension	121	83%	384	49%	34.8%	27.4% to 42.2%	12	80%
Hypercholesterolemia	81	56%	126	16%	39.9%	31.0% to 48.8%	8	53%
Obesity	51	35%	53	7%	28.5%	20.1% to 36.8%	3	20%
Smoking Past	57	39%	352	45%	-5.3%	-14.4% to 38%	5	33%
Smoking Current	20	14%	201	25%	-11.7%	-18.5% TO –4.9%	3	20%
Other	21	14%	DNA				0	0%
Renal Function:								
Creatinine (144)	1.7 ? 1.9 (0.4 – 11)		DNA				1.5 ? 1.2 (0.6 – 4.5)	
BUN (140)	34.0 ? 22.1 (7 – 139)		DNA				26.0 ? 13.3 (6 – 48)	
Poor Surgical Candidate:								
High Surgical Risk	66	46%	84	11%	35%	27% to 44%	2	13%
Absence of Venous Autologous Graft	47	32%	DNA				3	20%
Poor/No Distal	98	68%	DNA				12	80%
Any two Reasons	48	33%	DNA				2	13%
Any three Reasons	9	6%	DNA				0	0%

Notes: DNA = Data was not available for Control
Other (Risk Factors) = History of Infection, Neuropathy, Limb Pain, and Interventions in Limbs

Table 9 Baseline patient characteristics, Registry Group vs. Control Group

	Registry n = 145 n %	Control n = 789 n %	Difference [95%CI]
% Right Legs	75 (48%)	DNA	
Rutherford category:			
4	40 (28%)	240 (30%)	-2.8% [-10.8%, 5.1%]
5 or 6	105 (72%)	549 (70%)	2.8% [-5.1% , 10.8%]
5	94 (65%)	DNA	
6	11 (7%)	DNA	
CLI presentation:			
Rest pain	118 (81%)	729 (92%)	-11.0% [-17.6% , -4.4%]
Ulcers or Gangrene	105 (72%)	549 (70%)	2.8% [-5.1% , 10.8%]
Ulcers	96 (66%)	DNA	
Gangrene	39 (27%)	DNA	
Neuropathy	72 (50%)	DNA	
Duration of CLI (weeks)	25 ± 37 (1 - 261)	"AT LEAST 2 WEEKS"	
Location of ulcers/gangrene:	n %	n %	
Lower Leg(above ankle)	14 (9%)	DNA	
Ankle	12 (8%)	DNA	
Foot(below ankle)	65 (45%)	DNA	
Heel	17 (12%)	DNA	
Toe	33 (23%)	DNA	
Sole	3 (2%)	DNA	
Previous major amputation	0 (0%)	35 (4%)	-4.4% [-5.9%, -3.0%]
Previous minor amputation	18 (12%)	44 (6%)	6.8% [1.2% , 12.4%]
Post-procedure planned minor amp.	23 (16%)	DNA	
Amputation indicated (note 1)	56 (39%)	DNA	
Previous interventions (including bypass)	32 (22%)	176 (22%)	-0.2% [-7.6% , 7.1%]

NOTES:
1. "In the absence of intervention, would this patient be referred for amputation?"
DNA = data was not available for the Control group
CLI = critical limb ischemia

Locations of Vascular Lesions:	Lesions in the Registry Legs n = 423 n	 %
SFA	174	(41%)
Popliteal	64	(15%)
Tibio-peroneal trunk	51	(12%)
Anterior Tibial	38	(9%)
Peroneal	38	(9%)
Posterior Tibial	32	(8%)
Pedal	15	(4%)
Suprainguinal	10	(2%)
Graft	1	(0%)
	Registry Legs n = 155	
Lesions per limb	2.7 ± 1.4 (1 - 7)	
Lesion length (mm)*	61.5 ± 69.5 (1.5 - 500)	
Runoff vessels:	n	%
No vessel	46	(30%)
One vessel	62	(40%)
Two or more vessels	47	(30%)
Limbs had:	n	%
Stenoses alone in	14	(9%)
Occlusions alone in	32	(21%)
Stenoses and occlusions	109	(70%)

*Length of "lesions to treated," as recorded in the Pre-Treatment Diagnostic Angiography section of the Case Report Form

Table 10 Baseline vascular disease characteristics, Registry Legs

Table 11 Procedure information, Registry Legs

	Registry Legs n = 155		
Approach used: (3 missing)	n	%	
Antegrade	48	(31%)	
Contralateral	104	(67%)	
Mean number of guidewires used	1.8 ± 0.9		(0 - 5)
Failed guidewire crossing	13	(8%)	
Failure reasons (>1 reason is possible):	n	%	
Wire will not advance	9	(6%)	
Subintimal route	4	(3%)	
Poor backup support	2	(1%)	
Misalignment	2	(1%)	
Perforation	0	(0%)	
Other	2	(1%)	
Laser Information:	n	%	
Laser treatment delivered	153	(99%)	
Step-by-step technique	26	(17%)	
Mean number of laser catheters used	1.3 ± 0.7		(0 - 4)
Mean laser pulses delivered	5371 ± 5871		(375 - 39656)
Balloon Information:	n	%	
Balloon catheter used	149	(96%)	
Mean number of balloons	1.7 ± 0.8		(1 - 4)
Mean balloon diameter	4.0 ± 1.2		(1.5 - 8)
Stent Information:	n	%	
Stent implanted	70	(45%)	
	n	%	
Other procedures performed:	8	(5%)	
Iliac(s) treated	3	(2%)	
Rotational atherectomy with 1.25 burr	2	(1%)	
Aspiration catheter	1	(1%)	
Coronary angioplasty/stent	1	(1%)	
PTA of non-treatment leg	1	(1%)	
Mean Hospital stay, days	3.0 ± 5.1		(0 - 43)
Median hospital stay, days	1		

Note that laser treatment was delivered in 99% of the cases despite an 8% guidewire crossing failure rate. This is mainly due to the employment of the step-by-step technique unique to laser atherectomy procedures.

Table 12 Procedure Complications: Registry Legs by Group and Training Legs

Procedural Complications:	Registry Legs n= 155 n %	Training Legs n= 15 n %	Stented Legs n= 70 n %	Non-stented Legs n= 85 n %
Spasm	5 (3%)	0 (0%)	1 (1%)	4 (5%)
Major Dissection	6 (4%)	0 (0%)	3 (4%)	3 (4%)
Thrombus	5 (3%)	0 (0%)	4 (6%)	1 (1%)
Distal Embolization	5 (3%)	0 (0%)	3 (4%)	2 (2%)
Perforation (Note 1)	4 (3%)	2 (13%)	1 (1%)	3 (4%)
Need for urgent surgical revascularizton	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Sheath severed during manipulation (Note 2)	1 (1%)	0 (0%)	0 (0%)	1 (1%)
Other	6 (4%)	0 (0%)	1 (1%)	5 (6%)
Additional therapy required:	n %	n %	n %	n %
Balloon angioplasty	6 (4%)	0 (0%)	2 (3%)	4 (5%)
Bypass graft surgery	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Embolectomy	2 (1%)	0 (0%)	1 (1%)	1 (1%)
Endarterectomy	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Atherectomy	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Thrombolytic therapy	5 (3%)	0 (0%)	3 (4%)	2 (2%)
Thromboaspiration	3 (2%)	0 (0%)	3 (4%)	0 (0%)
Other	3 (2%)	0 (0%)	0 (0%)	3 (4%)

Notes:
1. One perforation led to compartment syndrome requiring anterior tibial/ peroneal fasciotomy of the leg.
2. The severed sheath required surgical removal.

Table 13 In Hospital Complications: Registry Legs by Group and Training Legs

	Registry Legs n= 155	Training Legs n= 15	Stented Legs n= 70	Non-stented Legs n= 85
	n %	n %	n %	n %
Reocclusion	2 (1%)	0 (0%)	1 (1%)	1 (1%)
Distal embolization	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Venous thrombosis	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Psuedoaneurysm	2 (1%)	0 (0%)	2 (3%)	0 (0%)
AV Fistula	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Renal failure	2 (1%)	1 (7%)	0 (0%)	2 (2%)
Bleeding	8 (5%)	0 (0%)	3 (4%)	5 (6%)
Puncture site	3 (2%)	0 (0%)	1 (1%)	2 (2%)
Retroperitoneal bleed	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Other	4 (3%)	0 (0%)	1 (1%)	3 (4%)
Infection	2 (1%)	0 (0%)	1 (1%)	1 (1%)
Other Complication	4 (3%)	0 (0%)	2 (3%)	2 (2%)
Additional therapy required				
Reintervention	2 (1%)	0 (0%)	1 (1%)	1 (1%)
Vascular repair	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Surgical revascularization	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Thrombolysis	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Transfusion (Note 1)	4 (3%)	0 (0%)	2 (3%)	2 (2%)
Dialysis	2 (1%)	1 (7%)	0 (0%)	2 (2%)
IV antibiotics	3 (2%)	0 (0%)	2 (3%)	1 (1%)
Other	5 (3%)	0 (0%)	3 (4%)	2 (2%)

Notes:
1. Three of the patients requiring a transfusion have a history of chronic anemia.

Procedural information on Stented Legs is broken out separately in Table 12. Stenting occurred more often in the superficial femoral artery (SFA), with the stent frequency decreasing as therapy reached towards the foot. A wide variety of stents were used, with the most frequently used stent being the nitinol Cordis Smart stent.

Table 14 Stent usage, Stented Legs

	Stented Legs n= 70		
Mean number of stents	1.9 ± 1.1		(1 - 5)
Mean total length of stents, mm	121 ± 94		(17 - 440)
Location of stents	133	(100%)	
SFA	87	(65%)	
Popliteal	26	(20%)	
Infrapopliteal	16	(12%)	
Other	4	(3%)	
Type of stents	145	(100%)	
BARD	7	(5%)	
BX Velocity	4	(3%)	
CORDIS SMART	54	(37%)	
DYNALINK	7	(5%)	
FLEX	7	(5%)	
INTRACOIL	12	(8%)	
JO	3	(2%)	
LUMINEX	3	(2%)	
MULTILINK	6	(4%)	
PALMAZ	2	(1%)	
PROTÉGÉ	8	(6%)	
RADIUS	4	(3%)	
UNKNOWN	5	(3%)	
Various BILIARY	2	(1%)	
Various other	17	(12%)	
WALL	4	(3%)	

Use of laser catheters is summarized in Table 13. A variety of sizes was required, ranging from 0.9 mm diameter to 2.5 mm.

Table 15 Laser catheters used, Registry Legs

Device Model #	Product Description	n
110-001	0.9 mm Extreme	16
110-002	0.9 mm Extreme	1
110-003	0.9 mm Vitesse	5
114-001	1.4 mm Extreme	1
114-009	1.4 mm Vitesse COS	24
117-007	1.7 mm Vitesse C	1
117-016	1.7 mm Vitesse COS	22
120-001	2.0 mm Extreme	10
120-008	2.0 mm Vitesse E	10
120-009	2.0 mm Vitesse COS	17
220-006	2.0 mm Extreme II	4
222-005	2.2 mm Extreme	54
223-001	2.3 mm Extreme II	1
225-004	2.5 mm Extreme	34
225-010	2.5 mm Extreme II	3
	Total:	203

Angiographic results, visually assessed by each investigator, are shown in Table 14.

Table 16 Angiographic results, Registry Legs

	Pre-Treatment Baseline % DS[1]		Post Laser % DS[1]		Final % DS[1]	
	Mean ± StdDev	Range %DS	Mean ± StdDev	Range %DS	Mean ± StdDev	Range %DS
SFA lesions						
Laser used	91 ± 13	(50 - 100)	56 ± 23	(0 - 100)	16 ± 25	(0 - 100)
Laser not used	100 ± 0	(100 - 100)	Not Applicable	Not Applicable	Not Applicable	Not Applicable
Popliteal lesions						
Laser used	94 ± 10	(70 - 100)	53 ± 26	(0 - 100)	14 ± 19	(0 - 100)
Laser not used	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable
Infrapopliteal lesions						
Laser used	92 ± 11	(50 - 100)	53 ± 28	(0 - 100)	24 ± 30	(0 - 100)
Laser not used	90 ± 0	(90 - 90)	Not Applicable	Not Applicable	Not Applicable	Not Applicable
All lesions	92 ± 12	(50 - 100)	55 ± 24	(0 - 100)	18 ± 26	(0 - 100)

NOTES:
1. %DS = percent stenosis, relative to vessel diameter.

Procedural results are arranged by group in Table 15. Procedural Success utilizes the final %DS determined by the investigator. Assessment of straight-line flow to the foot was also assessed by the investigator via angiography.

Table 17 Procedural and Clinical results by Group

	Registry Legs		Training Legs	
	Number Enrolled= 155		Number Enrolled= 15	
	n	%	n	%
Procedural success	132	(85%)	13	(87%)
Straight line flow established	138	(89%)	13	(87%)
Primary Endpoint	118	(76%)	12	(80%)

	Registry Group Stented Legs		Registry Group Non-stented Legs		p-value
	Number Enrolled= 70		Number Enrolled= 85		
	n	%	n	%	
Procedural success	65	(93%)	67	(79%)	0.013
Straight line flow established	67	(96%)	71	(84%)	0.019
Primary Endpoint	58	(83%)	60	(71%)	0.09

NOTES:
1. Procedural success: ≤50% residual stenosis (visual assessment) at conclusion of all LACI treatment steps, which may have included balloon angioplasty and/or stenting.
2. Straight line flow: patent superficial femoral artery, patent popliteal artery, and at least one patent infrapopliteal artery
3. Clinical success: Alive without major amputation at 6 months; equivalent to Primary Endpoint.
4. p-value by Fisher's Exact Test

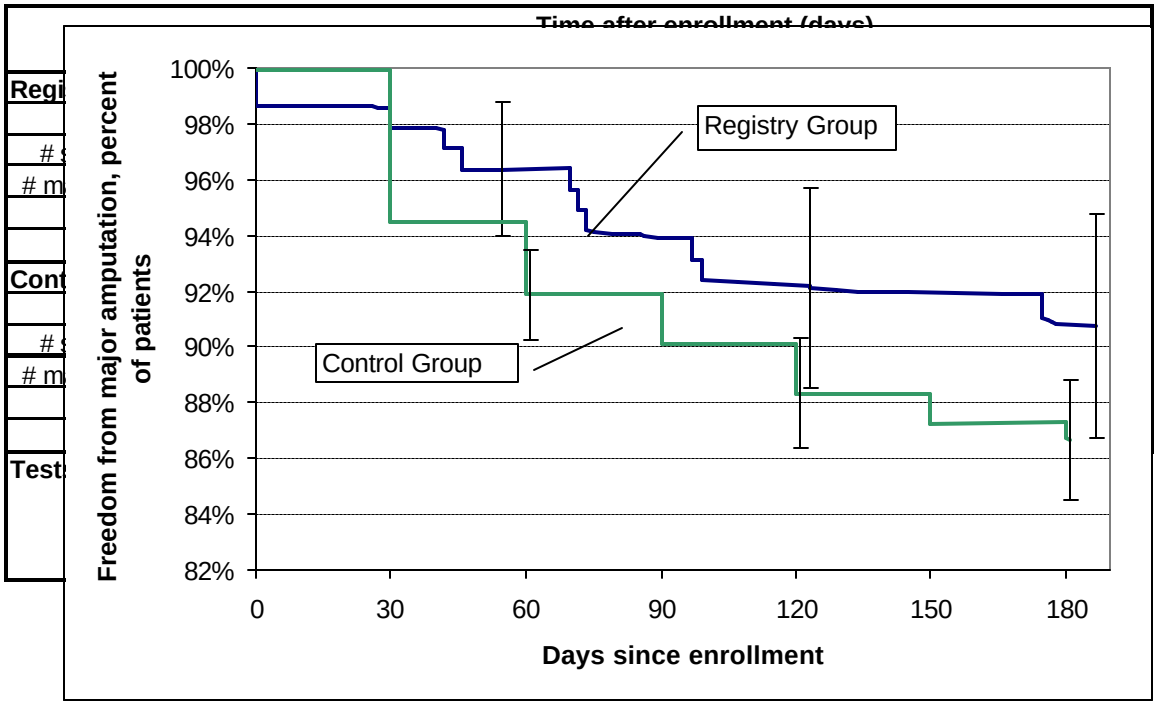
Table 18 Secondary endpoints, Registry Group

	Basis (note 1)	n	%
Angiographic procedural success (note 2)	limb	132	85%
Peripheral vascular endpoint (note 3)	limb	52	34%
Death during follow-up period (n=145 patients)	patient	15	10%
Incidence of minor amputation	limb	14	9%
Reduction in degree of planned amputation	limb		
Reduction in planned major amputation (note 4)		4	3%
Reduction in planned minor amputation (note 5)		2	2%
Surgical bypass	limb	3	2%
Surgical bypass to a previously unavailable site	limb	2	2%
Mean area percent healing of ulcers (note 6)	ulcer	85	50%

NOTES:

1. Limb basis n=155, patient basis n=145
2. Procedural success : 50% residual stenosis (visual assessment) at conclusion of all LACI treatment which may have included balloon angioplasty and/or stenting
3. Peripheral vascular endpoint: alive with major amputation or persistent CLI at 6 months
4. Amputation at or above the ankle
5. Amputation at or distal to the mid-foot
6. As determined by photo-morphography core lab, at 6 months

Figure 2 Kaplan-Meier plot, Freedom from Major Amputation, Registry Group & Control Group



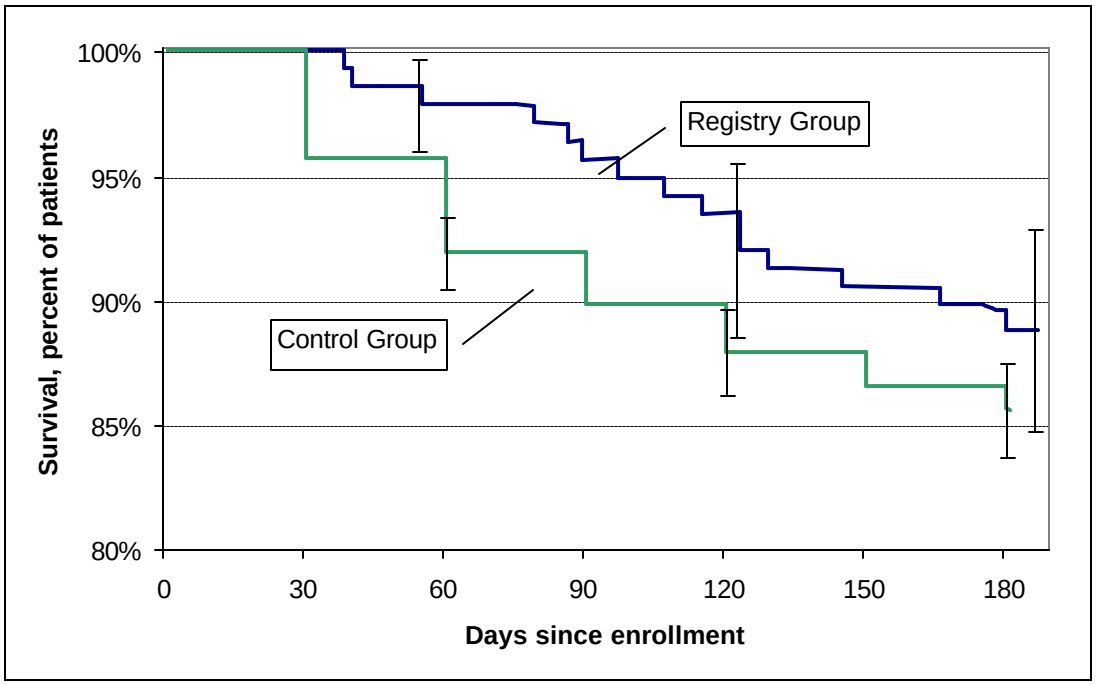


Figure 3 Kaplan-Meier plot, Death, Registry Group and Control Group

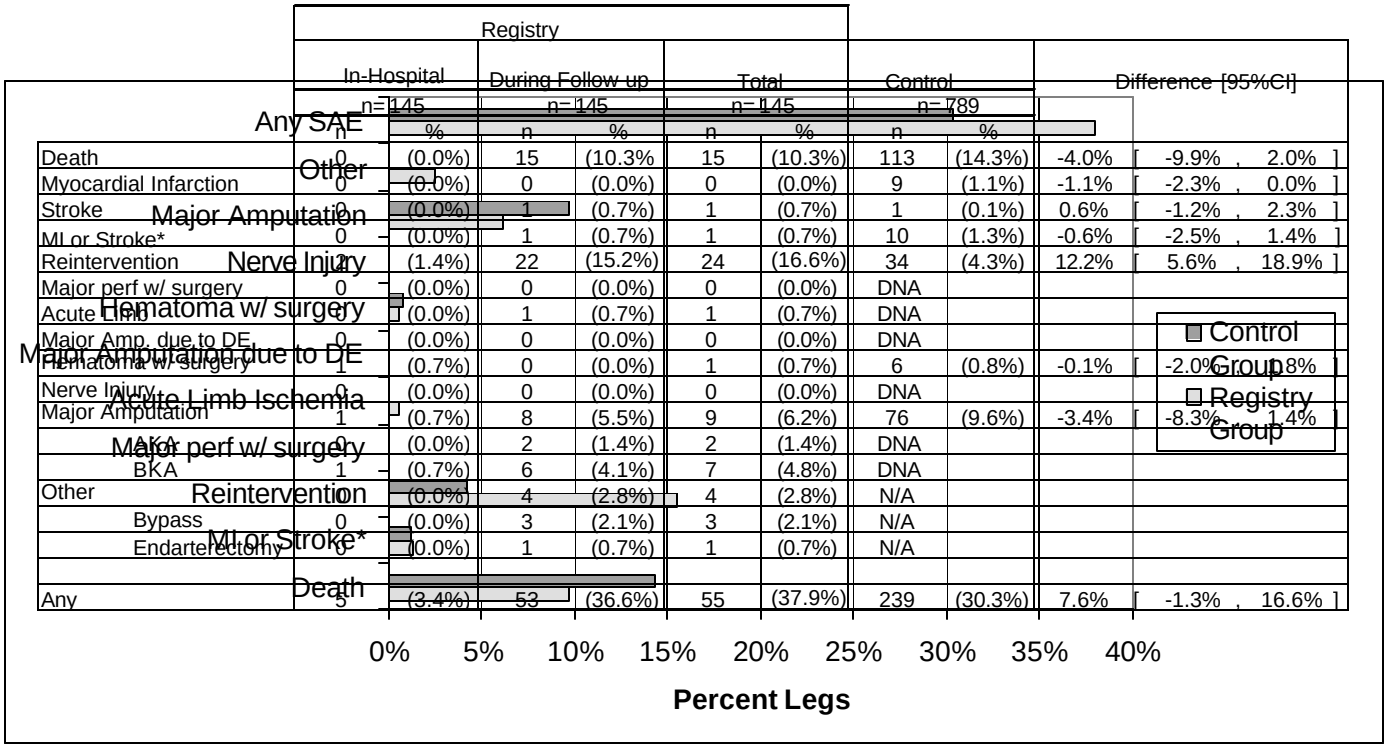
	Time after enrollment (days)						
	0	30	60	90	120	150	180
Registry Group							
# at risk	145	140	137	132	127	124	119
# in study	145	140	140	138	138	137	134
# deaths	0	0	3	6	11	13	15
% surviving	100%	100%	98%	96%	92%	91%	89%
1.5*%SEM	0.0%		1.8%		3.5%		4.1%
Control Group							
# at risk	789	755	725	706	691	680	670
# in study	789	789	789	786	786	786	783
# deaths	0	34	64	80	95	106	113
% surviving	100%	96%	92%	90%	88%	87%	86%
1.5*%SEM	0.0%		1.5%		1.7%		1.9%

Tests between Groups

time point	Chi-square	DegFrdm	p-value
180	0.75	1	0.38

Note: No deaths occurred during the LACI procedure, or due to a cause directly associated with LACI.

Figure 4 Adjudicated serious adverse events, Registry Group



NOTES:

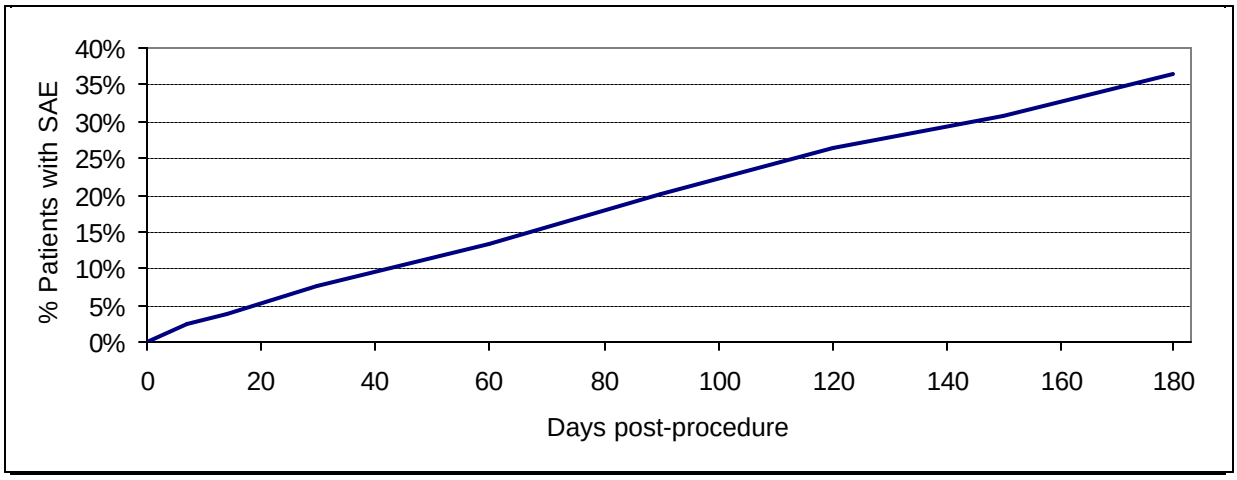
1. * nonfatal.
2. More than one event may have occurred to the same patient.
3. DNA = data is not available for the Control
4. N/A = not applicable, bypass and endarterectomy were part of the index treatment for some of the Control population.

Table 19 Adjudicated serious adverse events, Training Group

	In-Hospital n= 15		During Follow-up n= 15		Total n= 15	
	n	%	n	%	n	%
Death	0	(0.0%)	2	(13.3%)	2	(13.3%)
Myocardial Infarction (MI)*	0	(0.0%)	0	(0.0%)	0	(0.0%)
Stroke (CVA)*	0	(0.0%)	0	(0.0%)	0	(0.0%)
MI or Stroke*	0	(0.0%)	0	(0.0%)	0	(0.0%)
Reintervention	0	(0.0%)	0	(0.0%)	0	(0.0%)
Major perf w/ surgery	0	(0.0%)	0	(0.0%)	0	(0.0%)
Acute Limb Ischemia	0	(0.0%)	0	(0.0%)	0	(0.0%)
Major Amputation due to DE	0	(0.0%)	0	(0.0%)	0	(0.0%)
Hematoma w/ surgery	0	(0.0%)	0	(0.0%)	0	(0.0%)
Nerve Injury	0	(0.0%)	0	(0.0%)	0	(0.0%)
Major Amputation	0	(0.0%)	1	(6.7%)	1	(6.7%)
AKA	0	(0.0%)	0	(0.0%)	0	(0.0%)
BKA	0	(0.0%)	1	(6.7%)	1	(6.7%)
Other	0	(0.0%)	1	(6.7%)	1	(6.7%)
Bypass	0	(0.0%)	1	(6.7%)	1	(6.7%)
Endarterectomy	0	(0.0%)	0	(0.0%)	0	(0.0%)
Any SAE	0	(0.0%)	4	(26.7%)	4	(26.7%)

NOTES:
1. * nonfatal.
2. More than one event may have occurred to the same patient.

Figure 5 SAE rate versus time, All Patients



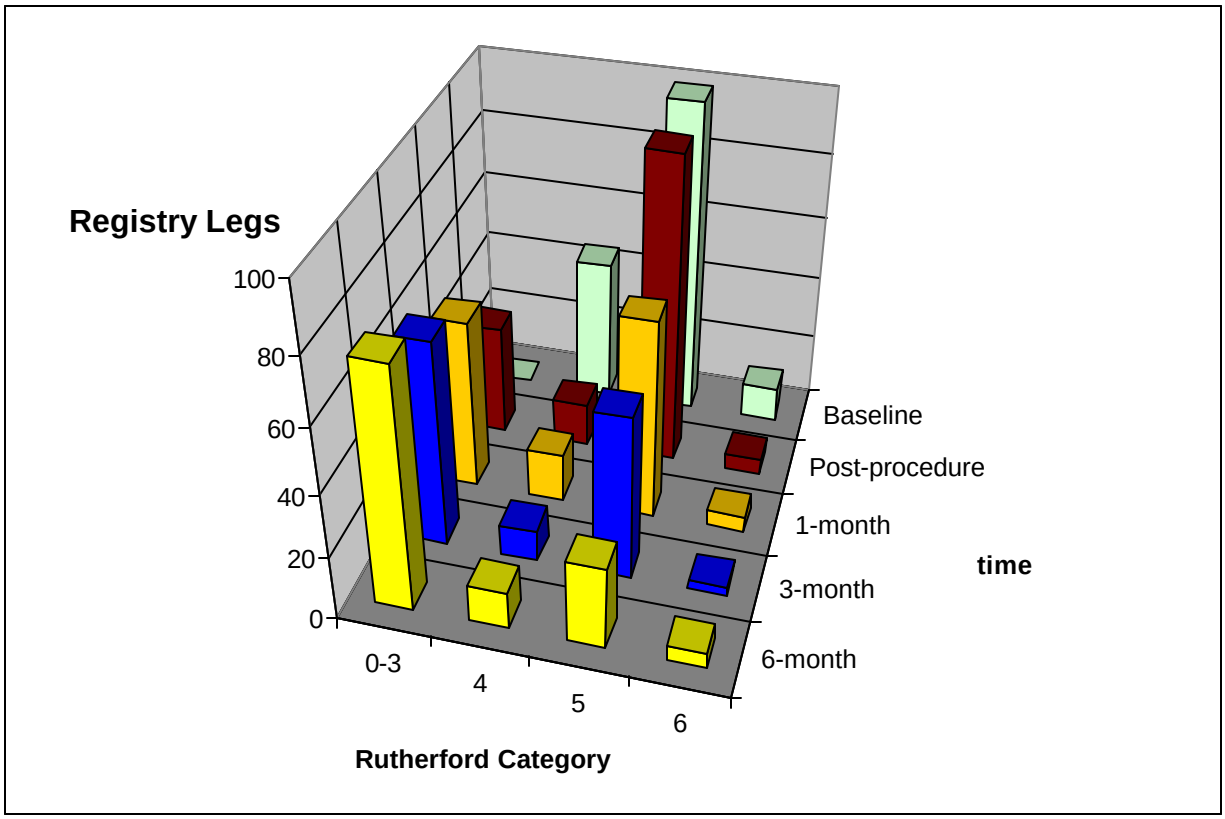
Interval ending	0	7	14	30	60	90	120	150	180
SAEs this interval		4	2	6	9	11	10	7	9
SAEs %/month		10.1%	7.5%	7.5%	5.7%	6.9%	6.3%	4.4%	5.7%
cumulative SAEs	0	4	6	12	21	32	42	49	58
% Patients with SAE	0	2.5%	3.8%	7.5%	13%	20%	26%	31%	36%

Table 20 Predictors of mortality and major amputation

Univariate Predictors of Outcomes				
Variables associated with major amputation				
	Variable	**p-value**	**O.R.**	**[95% CI]**
	Category 6 leg	0.03	6.4	[1.4 , 29]
	Previous minor amputation	0.05	3.6	[1.02 , 13]
	Diabetes	0.1	5.7	[0.7 , 45]
	Category 5-6 leg	0.18	0.44	[0.55 , 35]
	Gender	0.76	0.7	[0.2 , 2.4]
	Procedure success	0.19	0.4	[0.1 , 1.7]
	Straight line flow established	0.3	0.5	[0.09 , 2.3]
	Stented leg	0.35	0.4	[0.11 , 1.7]
Variables associated with death				
	Age	0.03		
	Category 5-6 leg	0.07	6	[0.76 , 47]
	History of CAD	0.1	3.1	[0.93 , 10]
	Gender	0.8	0.75	[0.26 , 2.2]

p-values from continuity-corrected Chi-square, or Fisher's Exact if a cell count <5. P-value for age by 2-sided T-test. O.R. = Odds Ratio.
CAD = coronary artery disease.

Figure 6 Rutherford Category distribution versus time, Registry Legs



Rutherford Category	0-3	4	5	6
Baseline (n=155)	0	45	99	11
Post-procedure	35	14	97	5
1-month	54	15	63	5
3-month	65	10	52	3
6-month	75	12	26	5

Changes in Rutherford category are summarized at 6 months in Figure 7. Of the surviving limbs, 69% improved ?1 category, 27% were stable, and 4% worsened by ?1 categories. The 37 missing observations of Rutherford Category at 6 months are due to: death in 17 limbs, 11 lost-to-follow-up limbs, and 9 limbs surviving with major amputation.

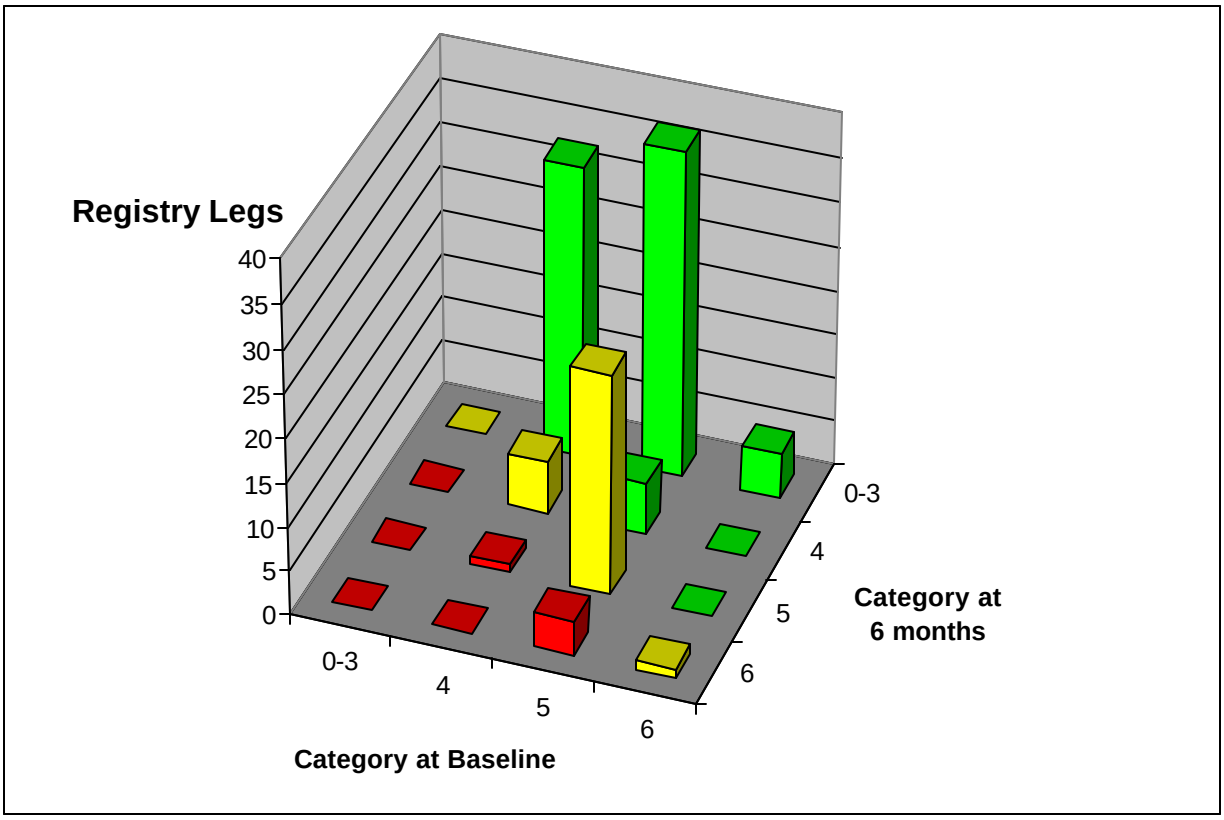


Figure 7 Rutherford Category Outcomes, Registry Legs

		Rutherford Category at Baseline				
		0-3	4	5	6	total
Category at 6 months						
	0-3	0 (0%)	33 (21%)	37 (24%)	5 (3%)	75 (48%)
	4	0 (0%)	6 (4%)	6 (4%)	0 (0%)	12 (8%)
	5	0 (0%)	1 (1%)	25 (16%)	0 (0%)	26 (17%)
	6	0 (0%)	0 (0%)	4 (3%)	1 (1%)	5 (3%)
	missing	0 (0%)	5 (3%)	27 (17%)	5 (3%)	37 (24%)
Total		0	45	99	11	155

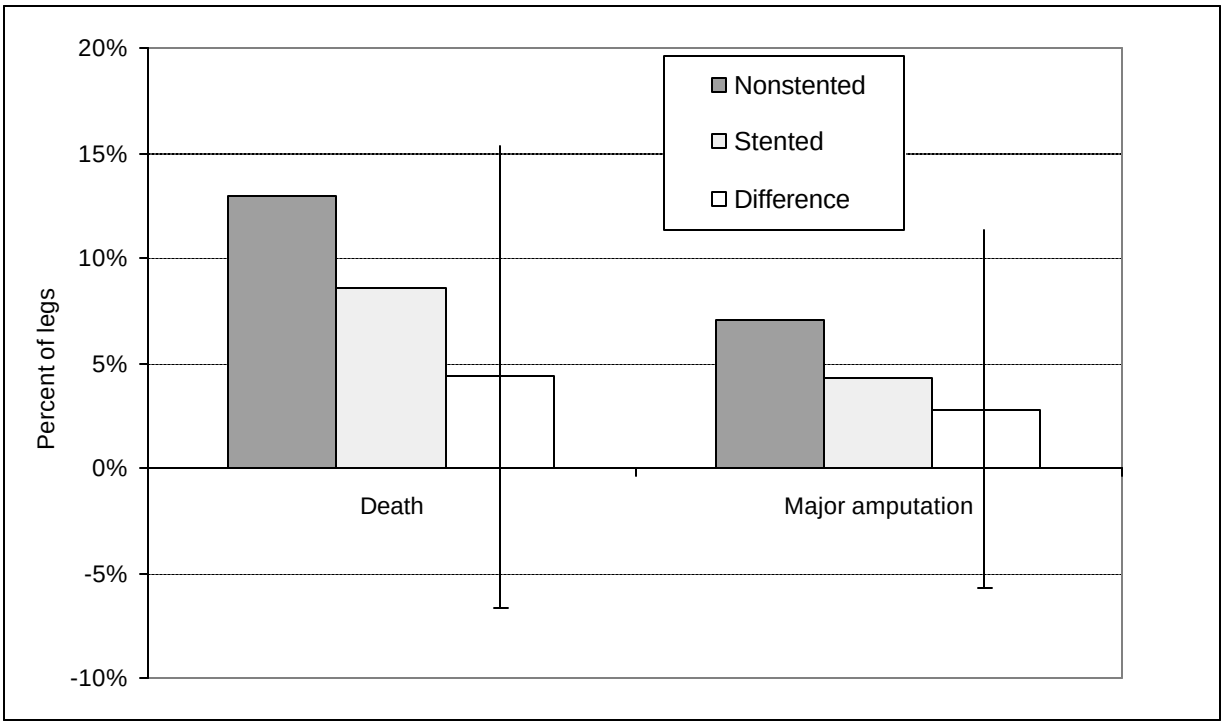
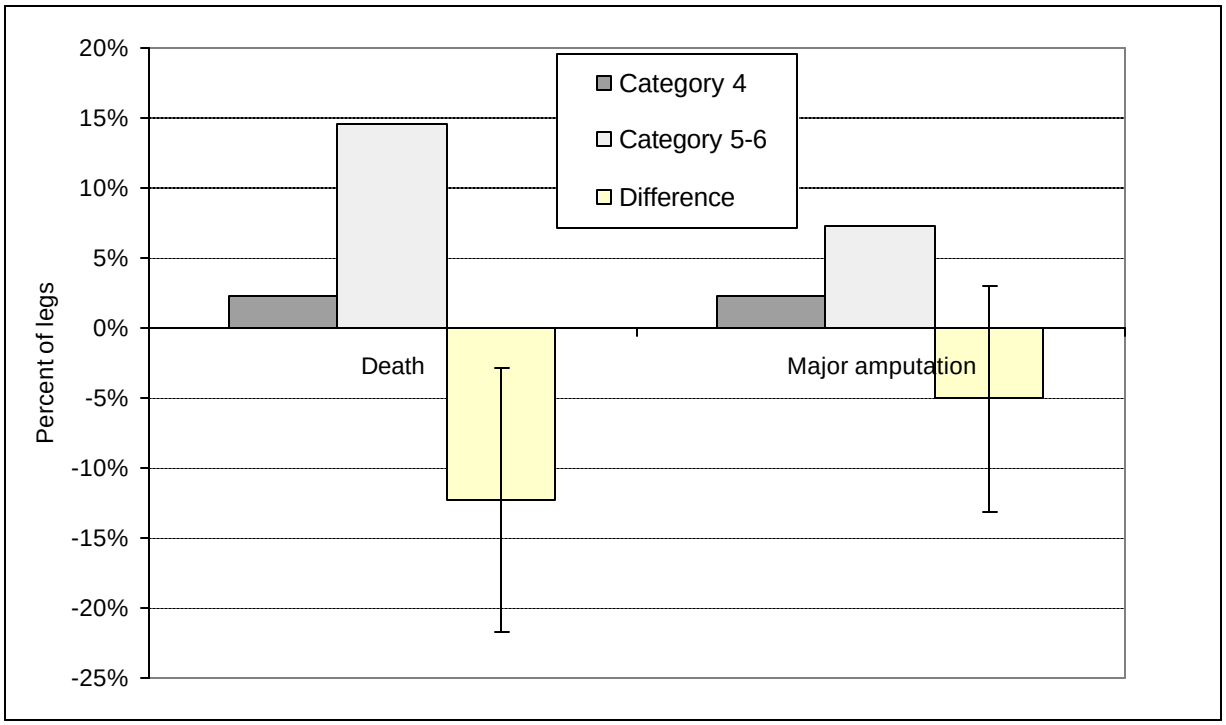


Figure 8 Outcomes in Stented Legs versus Non-stented Legs

	Nonstented Legs	Stented Legs	Difference [95%CI]
Enrolled legs	85 (100%)	70 (100%)	
Died	11 (13%)	6 (9%)	4% [-6.6% , 15.4%]
Lost to F-U	8 (9%)	3 (4%)	5% [-4.0% , 14.2%]
Finished Study	66 (78%)	61 (87%)	-9% [-22.6% , 3.6%]
Bypass	3 (4%)	0 (0%)	4% [-1.7% , 8.8%]
Major Amputation	6 (7%)	3 (4%)	3% [-5.8% , 11.3%]
Primary endpoint	60 (71%)	58 (83%)	-12% [-26.7% , 2.1%]

NOTES:
Difference = LACI-Control = p1-p2. SEM=sqrt(p1q1/n1 + p2q2/n2). D=SEM*1.96.
Corr= (1/n1 + 1/n2)/2. Lo=Difference-D-Corr. Hi=Difference+D+Corr.
Finished Study: enrolled legs minus died, lost-to-follow-up
Primary endpoint: limbs without major amputation, death, or lost-to-follow-up

Figure 9 Outcomes in Category 4 Legs versus Category 5-6 Legs n=155



	Category 4 Legs		Category 5-6 Legs		Difference [95%CI]		
Enrolled legs	45	(100%)	110	(100%)			
Died	1	(2%)	16	(15%)	-12% [	-21.8%	-2.9%]
Lost to F-U	2	(4%)	9	(8%)	-4% [	-13.2%	5.7%]
Finished Study	42	(93%)	85	(77%)	16% [	3.8%	28.3%]
Bypass	0	(0%)	3	(3%)	-3% [	-7.3%	1.9%]
Major Amputation	1	(2%)	8	(7%)	-5% [	-13.1%	3.0%]
Primary endpoint	41	(91%)	77	(70%)	21% [	7.6%	34.6%]

NOTES:
Difference = LACI-Control = p1-p2. SEM=sqrt(p1q1/n1 + p2q2/n2). D=SEM*1.96.
Corr= (1/n1 + 1/n2)/2. Lo=Difference-D-Corr. Hi=Difference+D+Corr.
Finished Study: enrolled legs minus died, lost-to-follow-up
Peripheral endpoint: alive with major amputation or persistent CLI at 6 months
Primary endpoint: limbs without major amputation, death, or lost-to-follow-up

Table 21 Narrative of cases with SAEs

	DEATHS OCCURRING IN LACI REGISTRY GROUP
AHI 004; WATGL	Female patient, 83 years of age, presented with Rutherford classification 5, on 10 Sep 01 and expired on 11 Jan 02. Two (2) gangrenous, right toes were noted at screening, along with severe stenoses in the right anterior tibial and peroneal arteries. Debulking the lesions with a laser catheter followed by adjunctive balloon angioplasty, lead to clinical success (10-30% residual stenosis). Part of the great toe, and the 4th toe, of the right foot were amputated at the 1-month follow up examination. The patient was hospitalized and treated for left pleural effusion on 10 Oct 01. The "chronically ill" woman was again hospitalized for 10 days from 18 Dec 01, through 28 Dec 01, and her right leg was amputated below the knee. The nursing care facility physician referred her to the hospital for a brief examination of the amputation site on 31 Dec 01, and she was released that same day. Congestive heart failure (chronic pleural effusion) was noted by the nursing care staff early on 11 Jan 02, and the patient expired soon thereafter, on 11 Jan 02.
AHI 013 MURMA	Female patient, 67 years of age with diabetes, presented with Rutherford classification 4 and an ulceration on the left heel, on 10 Dec 01 and expired on 15 Jun 02. Stenoses of 60 and 70% in the left SFA and anterior tibial arteries, respectively, were successfully reduced to 0 and 30% after laser treatment and adjunctive balloon angioplasty. On 27 Feb 02, she entered the hospital through the emergency room, having stepped on a nail, and the left great toe was amputated due to uncontrolled sepsis and gangrene, in spite of IV administration of antibiotics. The patient entered hospice care on 5 Jun 02, for wound care secondary to a lack of healing at the left great toe amputation site. Hospice representatives listed failure to thrive, along with cardiac issues, as contributing factors to death on 15 Jun 02.
FRA 003 LOEHE	An 81-year diabetic male presented on 26 Feb 02, with Rutherford class 5 critical ischemia in the left leg, and the lesions were successfully treated via the LACI procedure. As of 17 Mar 02, the patient had developed pneumonia, and was rehospitalized. The patient died on 7 Apr 02, of cardiac insufficiency related to the pneumonia.
GRE 003 WALLO	Female patient, 83 years of age, presented with Rutherford category 5, and total occlusions in the SFA and posterior tibial arteries of the left leg, on 12 Jun 01, and died on 5 Oct 01. Clinical success was noted after debulking with a laser catheter, adjunctive balloon angioplasty, and stent placement, with stenoses reduced to 20-40%. The patient was hospitalized on 19 Oct 01, with congestive heart failure and respiratory distress. Her condition worsened with respect to severe cardiomyopathy until her death on 5 Oct 01.
GRE 009 NEACO	This 72-year old women, with a history of diabetes, presented on 7 Nov 01, with Rutherford category 5 CLI. Multiple stenoses in the right leg were treated with procedural success. On 12 Nov 01 the patient was again hospitalized for amputation of gangrenous toe on left foot. Persistent nausea was cause for hospitalization again between 3 Dec 01 and 8 Dec 01, and again from 23 Dec 01 through 18 Jan 02, during which the left leg was amputated below the knee.

	Myocardial infarction and death occurred on 10 Mar 02.
	DEATHS OCCURRING IN LACI REGISTRY GROUP - CONTINUED
GRE 010 WEHMA	Female patient, 87 years of age, presented on 8 Jan 02, with Rutherford classification 5, and non-healing ulcerations due to total occlusion in the right distal SFA and tibial-peroneal trunk, and expired on 23 Jun 02. Laser treatment and balloon angioplasty led to clinical success with residual stenoses of 0-10% in treated lesions. Patient was hospitalized between 21 Feb 02, and 1 Mar 02, for treatment of thrombosis in right leg. On 20 Jun 02, the patient was admitted with symptoms of sepsis, leading to death on 23 Jun 02. It was noted that ulcerations on patient's feet were healed at time of death.
GRE 012 HARMI	Diabetic male patient, 59 years of age, presented on 17 Jan 02, in Rutherford category 4, ulceration on left great toe, and 50-90% stenosis in four (4) lesions from the proximal SFA to the popliteal artery, and expired on 11 Jun 02. In spite of clinical success, with stenoses reduced to 0-10%, renal failure and bacterial sepsis lead to death while on dialysis 11 Jun 02.
LAN 005 ZIBBE	Male, 85 year old patient, was screened on 3 Jul 01, and died on 30 Sep 01. He presented with Rutherford category 5 symptoms, including ulceration on the right foot. Total occlusion of the proximal SFA was treated both laser and balloon angioplasty, followed by stent placement. Clinical success with 10% residual stenosis was noted. Myocardial infarction and cardiac arrest lead to death on 30 Sep 01.
LAN 007 CANJO	Male patient, 76 years of age, with non-healing ulcers on the right lower extremities, presented in Rutherford category 6 on 17 Jul 01. Total occlusions in the tibial and peroneal arteries were successfully opened, with <50% residual stenosis. The patient's leg wounds healed, but sepsis lead to death on 23 Nov 01.
LEI 026 and 027 PEUMA	Both legs of this 76 year old women were treated with the LACI technique, on 15 Apr 02. She presented with Rutherford category 5 ischemia, and non-healing ulcers. Procedural success was achieved for both limbs. On 31 Jul 02, the patient went in for a planned CABG operation, during which she suffered a stroke, and subsequently died. Please notice that the investigator filed four (4) SAE forms documenting this single event: relating to the right leg - one form for the CABG and one for the death due to associated stroke; relating to the left leg - one form for the CABG and one for the death due to associated stroke. This single SAE was judged to be unrelated to the LACI procedure.
RIV 004 SECAR	Male, 82-year-old patient, presented on 22 Aug 01, with total occlusions in the posterior and distal posterior tibial arteries, Rutherford classification 5, and a history of diabetes mellitus with renal failure. The patient expired on 27 Nov 01. Laser atherectomy, balloon angioplasty, and stenting in the left leg resulted in reduction to 20% residual stenosis (clinical success). Persistent gangrene lead to the amputation of two (2) toes on 5 Oct 01. The patient was re-admitted on 31 Oct 01, for infection at amputation site, and re-interventions were performed including rotablator debulking, balloon angioplasty, and stent placement. On-going infection required continual hospitalization until death on 27 Nov 01.

	DEATHS OCCURRING IN LACI REGISTRY GROUP - CONTINUED
RIV 007 MOWRO	On 1 Mar 02, a 72 year old male patient presented with Rutherford 5 chronic limb ischemia, ulcerations on the right foot, and diabetes. Total occlusions were successfully treated and the patient was discharged. On 25 Apr 02, the patient expired with pneumonia exacerbated by peripheral disease.
SJO 003 CULAG	Seventy-seven (77) year old diabetic female, presented with Rutherford category 5, ulcerations, and gangrene on right foot, 3 Jan 02. Total occlusions in SFA were not opened using laser atherectomy, and no adjunctive treatment was attempted. Femoral popliteal bypass surgery on 21 Jan 02 lead to complications including congestive heart failure, and the patient expired on 10 Feb 02.
ZEL 010 & ZEL 011 KIREL	Female diabetic patient, 74 years of age, presented with ulcerations and gangrene on both feet, on 31 Jan 02. Tibial arteries on the right limb were successfully treated. On 6 Feb 02, the same patient was treated on the left limb reducing stenosis of the tibial arteries from 90% to 10%. Patient was hospitalized on 5 Apr 02, for sepsis associated with catheterization for renal failure. Patient's status deteriorated until death on 20 Apr 02.
ZEL 019 SEUHA	A diabetic male, 73 years of age, presented on 8 Apr 02, in Rutherford category 5 with ulcerations on the right foot. LACI procedures failed to open total occlusions in the SFA, and the patient was discharged on 10 Apr 02. On 3 Jul 02, the patient expired due to multiple organ failure associated with septic shock.

	DEATHS OCCURRING IN TRAINING GROUP
SLM T03 ZOLBE	Seventy-seven (77) year old woman presented on 1 Aug 01, with Rutherford category 5 CLI and ulceration on the right foot. Total occlusion of the distal SFA was successfully opened with 0% residual stenosis using laser catheter treatment only. On 6 Aug 01 the patient expired due to cardiopulmonary arrest, probably secondary to pulmonary embolism.
SJO T02 RIOMA	Woman, 74 years old with diabetes, was screened on 20 Sep 02 with ulcerations on the left extremities, Rutherford category 5, and total occlusions. Occlusions were not re-opened with either laser or balloon angioplasty catheters. Below the knee amputation on 18 Oct 02 was followed by sudden death on 27 Nov 02.

	DEATHS OCCURRING OUTSIDE OF 6-MONTH STUDY TIME FRAME
GRE 004 BOUTE (Death outside of Time Frame)	Man, 53 years old, presented with Rutherford category 5 CLI on 20 JUL 01. The individual had several total occlusions from the profunda femoris to the peroneal artery in the left leg, with ulcerations. Procedural success was achieved after both laser and balloon therapy, with all treated lesions showing less than 50% stenosis. By 10 Jan 02, complete healing was noted in conjunction with the 6 months follow up examination. The patient died on 9 May 02, after completion of LACI follow up and study exit.
GRE 005 JENSA (Death outside of Time Frame)	On 24 Aug 01, this 60 year old diabetic female presented with Rutherford class 5 CLI, with accompanying gangrenous ulcerations on the left foot. LACI treatment of the tibial arteries results in procedural success, stenosis being reduced from 90% to 30%. However, the patient required hospitalization from 21 Sep 01 through 6 Oct 02, and finally amputation below the knee on 5 Nov 01, and did not complete the LACI study. The patient suffered a myocardial infarction, and expired on 12 Jul 02, outside the follow up time frame for study.
ZEL 001 PRZAU (Death outside of Time Frame)	A 64-year-old woman presented with Rutherford class 5 symptoms and non-healing ulcers on the right foot, on 5 Dec 01. The woman likewise showed severe stenosis (99%) of the right popliteal and anterior tibial arteries. Procedural success was achieved with the LACI treatment, reducing residual stenosis to 20%. During the post-procedure hospital the right foot required a transmetatarsal amputation due to persistent infection. The patient was discharged on 20 Dec 01. On 13 Oct 02, the patient passed away after on-going problems with infection in the left foot.

	PATIENTS NOT COMPLETING STUDY
AHI 005 COATO	Diabetic male patient, 59 years old, with Rutherford category 4 symptoms and stenosis in left tibial trunk and anterior arteries, was treated without success on 16 Oct 01. Extravasion was noted, and surgical intervention was required, immediately after the LACI procedure. Patient moved, stating that he took release papers with him. No further records forthcoming.
AHI 024 KOEEL	Female patient, 91 years old, presented with stenosis in left SFA and Rutherford category 6 on 17 Apr 02. LACI treatment was successful, and the patient was discharged without pain. Three month follow up data shows improvement to Rutherford category 3. Daughter stated that she could no longer bring patient in for follow up after that time.
FRA 001 BELIE	Female patient, 73 years of age, was treated on 11 Feb 02. Procedural success was achieved in the right leg. Study exit notes, dated 10 Dec 02, indicate that the patient did not answer written invitations for follow up exams. Patient has no primary care physician and no telephone.
FRA 002 VOHAN	Male patient, 68 years old, presented on 13 Feb 02 with Rutherford classification 5 critical limb ischemia (CLI), non-healing ulcers and gangrene, on the left ankle. After procedural success, the patient was discharged the next day, 14 Feb 02. At 1 month post-procedure, the patient returned for a routine follow-up visit, having improved to Rutherford class 2. The patient returned again on 18 Jun 02, only after receiving a written invitation. Though no rest pain is recorded, Rutherford classification 5 was recorded at that time, and patient was noted as having high co-morbidity and severe immobility. Patient refused any further examination and exit papers were completed on 23 Oct 02.
LEI 001 ABELO	Male, 70 years of age, presented on 17 Jan 02, in Rutherford class 5, with gangrene and ulcerations on the right foot. LACI treatment was successful, and the patient was discharged on 18 Jan 02. Exit records show that the patient was contacted via telephone at least six (6) times, but he refused follow up because, "he feels good and has no pain." Exit records were completed 31 Jul 02.
LEI 002 LAUJO	Male, 72 years of age, was unsuccessfully treated on 22 Jan 02, for Rutherford category 6 CLI, with non-healing ulcers on the right foot and toes. The patient's doctor was contacted during February '02, and three letters were sent to the patient requesting follow up. The patient did not respond and Study Exit papers were completed on 31 Jul 02.
LEI 004 GLACH	Women, 87 years of age, was screened and treated for Rutherford class 5 CLI on 18 Jan 02. The procedure was successful. The patient was unavailable to receive calls on March 10, 15, and 23, and during April, 2002. Two (2) letters were sent to the patient, but were returned undeliverable, due to the fact that the patient moved.
LEI 016 REIGI	Female patient, 84 years old, presented with Rutherford category 6 CLI in the right leg on 18 Mar 02, and was successfully treated using the LACI technique. She was lost to follow up due to moving without leaving any forwarding information, as noted on the Study Exit form completed 30 Jul 02.

	PATIENTS NOT COMPLETING STUDY - CONTINUED
LEI 028 ECUMA	Seventy-six (76) year old female patient was treated for ischemia in the left leg on 17 Apr 02. One month and 3-month follow up data were collected during visits to the investigators clinical offices. However exit documentation, dated 18 Dec 02, notes that the patient did not answer either telephone calls or letters regarding the 6 month follow up. Her doctor does not know how to contact her.
RIV 005 GLAJE	On 23 Aug 01, a 46 year old male presented with Rutherford category 5 CLI in the right leg, and procedural success was achieved with LACI. Minor amputation was required on 26 Oct 01, due to persistent gangrene. This diabetic patient with renal failure, eventually required coronary bypass surgery, and was discharged to extended care on 10 Dec 01. Study exit papers dated 6 Nov 01, and signed on 8 May 02, state that the patient was contacted and stated "no longer a patient of Dr. Ansels." A letter was sent with no response.
ZEL 001 PRZAU	Patient, female 64 years old, entered the LACI study on 5 Dec 01, with Rutherford class 5 CLI in the right leg. Procedural success was followed by discharge on 20 Dec 01. Amputation of the right foot was necessary on 18 Dec 01, due to persistent infection. The patient completed 3-month follow up examinations in March '02, but did not respond to phone calls or letters after that time, according to the Study Exit form competed on 16 Oct 02. The patient expired on 13 Oct 02, outside the 6-month time frame established for the LACI protocol.
AHI T27 JOHEL	Male patient, 80 years of age, was treated on 17 Apr 01. Procedural success was achieved in the left leg. Candidacy of this patient for LACI was questioned during on-site monitoring, and his left limb was moved to the training group as a result. Events related to hiatal hernia while hospitalized were noted. The patient called after discharge to inform investigators that he had moved to Minnesota, and would be unable to keep follow up appointments.
SLM T01 WAIES	This 77 year old female, was screened and treated under the LACI protocol on 10 Jul 01. Non-healing ulcers and Rutherford category 5 were noted at that time. Procedural success was achieved on the right leg, and the patient was discharged on 16 Jul 01. 1-month follow up indicates that amputation of a toe and surgical bypass were performed, and the patient's status had improved to Rutherford category 0, no CLI. The patient refuse all further follow up visits, as noted on 23 Jul 02.

	ADJUDICATED "TRUE" LACI SERIOUS ADVERSE EVENTS (NON-DEATH) RELATED TO LACI PROCEDURE – REGISTRY GROUP
AHI 009 FISAL	On 1 Nov 01, a 69 year old male diabetic underwent LACI for left leg ischemia. Reocclusion occurred after procedural success, and required re-intervention with "angiojet" and stent placement. This reintervention was recorded as an in-hospital complication, and then later adjudicated as an SAE.
CAR 005 MCCRO	Seventy-eight (78) year old male, presenting with Rutherford category 5 limb ischemia, was unsuccessfully treated on 14 Mar 02, using LACI techniques on occlusions in the right leg. Disease progression led to bypass surgery on the limb, dated 9 May 02. A previously unavailable site was used for the bypass.
GLE 002 PARES	SAE #1 – Coronary revascularization was adjudicated as a non-SAE. Automatically Adjudicated SAE – Seventy-seven (77) year old female patient, with diabetes and severe peripheral vascular disease in the right leg, received LACI on 31 Jan 02. On 3 May 02, follow up data documents a repeat angioplasty due to restenosis. This reintervention was later adjudicated as an SAE. SAE #2 – The patient required re-intervention on 3 Jul 02, near the time of her 6-month follow up. Reintervention included both laser and balloon angioplasty. Improved flow was not visualized in the anterior tibial artery. SAE #3 – Continued ischemia required rehospitalization on 5 Jul 02, followed by below the knee amputation on 9 Jul 02. These SAE's have been deemed related to LACI.
GLE 005 LAZYO	A 64-year-old diabetic man presented on 2 Feb 02 with ulcerations, a necrotic toe, and Rutherford 6 critical ischemia. LACI was not successful on the right leg. The gentleman visited the emergency room on 30 Apr 02, showing poor healing of the wound due to minor amputation. He was admitted to the hospital on 1 May 02, suffered a below the knee amputation on 3 May 02, and was discharged on 7 May 02. This was adjudicated as related to LACI.
GRE 001 MILAL	On 16 Mar 01, a 78 year old male patient presented with Rutherford category 5 ischemia in the right leg. LACI did not achieve procedural success. Endarterectomy was performed on 4 Aug 01. This surgical reintervention was later adjudicated as an SAE.
GRE 005 JENSA	A 60 year old woman, having peripheral arterial disease in both legs, was treated on her left leg using LACI techniques, on 20 Jul 01. On 5 Nov 01, her left leg was amputated below the knee to alleviate non-healing wounds. This SAE was judged related to the LACI procedure. The death in conjunction with myocardial infarction (see above) was not considered to be related to LACI, and was outside the 6 month time frame for LACI follow up.
GRE 006 SPEJO	Procedural success was achieved for LACI treatment of the left leg of a 77 year old man, on 31 Aug 01. However, repeat angioplasty was deemed necessary prior to 6 month follow up, due to restenosis. This reintervention was later adjudicated as an SAE.
GRE 007 GOLMI	SAE #1 – An 83-year-old man was treated using LACI on 11 Sep 01. LACI achieved procedural success, reducing stenosis in the left leg to 30%. However the patient required prolonged hospitalization, surgical repair for retroperitoneal bleeding associated with hematoma, on 20 Sep 01. This SAE was judged to be

	related to LACI. SAE #2 - Finally above the knee amputation was necessary on 3 Oct 01. This SAE was judged to be related to LACI.

	ADJUDICATED "TRUE" LACI SERIOUS ADVERSE EVENTS (NON-DEATH) RELATED TO LACI PROCEDURE – REGISTRY GROUP CONTINUED
GRE 008 KIRJO	Male patient, 86 years old, was successfully treated for ischemia in the left leg on 5 Oct 01. Study exit was documented on 5 Apr 02. Shortly thereafter reintervention was documented, between the exit date of 5 Apr 02, and 13 May 02. In spite of the study exit prior to the incident, this SAE was judged to be related to LACI.
GRE 009 NEACO	This 72-year old women, with a history of diabetes, presented on 7 Nov 01, and multiple stenoses in the right leg were treated with procedural success. On 12 Nov 01 the patient was again hospitalized for amputation of gangrenous toe on left foot. Persistent nausea was cause for hospitalization again between 23 Dec 01 and 18 Jan 02, during which the left leg was amputated below the knee. The amputation was adjudicated as procedurally related to LACI, but the death (see above) due to myocardial infarction was not.
GRE 011 WILBE	This 77 year old diabetic woman was successfully treated for left leg ischemia on 8 Jan 02. Prior to 3-month follow up, a restenosis at the origin of the SFA required repeat angioplasty. This reintervention was later adjudicated as an SAE.
GRE 016 MCKPA	The 73 year old male patient was treated on 12 Mar 02. LACI was successful in the right leg, in spite of major dissection, which was rectified with "prolonged" balloon angioplasty. Not long before the 6-month follow up the patient experienced severe cold and numbness in the left foot, coming into the emergency room for treatment. On 25 Aug 02, repeat angioplasty was helpful and the patient was discharged. This event was adjudged relevant to LACI.
GRE 017 WESDO	On 14 Mar 02, this 56 year old man underwent successful LACI on the right leg. Physicians reintervened with thrombolytic drugs during a re-hospitalization between 4 Apr 02, and 10 Apr 02. This event was judged as a true SAE related to LACI.
LAN 002 DICJO	A male patient 76 years of age received LACI intervention on 20 Apr 01, for total occlusions in the left leg. The procedure was not successful. Below the knee amputation was necessary on 25 Apr 01. This SAE was judged to be relevant to LACI
LAN 004 MERMA	A 69 year old male was successfully treated on the left leg using LACI techniques, on 15 Jun 01. Reintervention, including a bypass graft, was necessary between 19 and 24 Dec 01. Adjudication shows this event to have been related to LACI.
LEI 008 RICCH	A 71-year-old diabetic woman presented on 20 Feb 02 with Rutherford category 4 symptoms of critical ischemia. Her right leg was successfully treated using the LACI procedure. Restenosis lead to repeat angioplasty on 26 Jun 02. This reintervention was later adjudicated as an SAE.
LEI 010 RICCH	Female patient, 71 years of age, was successfully treated on 21 Feb 02, using LACI on the left leg. Between 23 and 24 May 02, reintervention was necessary due to restenosis. This event was related to the LACI procedure. Note: Same patient as LEI 008

	ADJUDICATED "TRUE" LACI SERIOUS ADVERSE EVENTS (NON-DEATH) RELATED TO LACI PROCEDURE – REGISTRY GROUP CONTINUED
LEI 014 ROSIR	An 81 year old female patient underwent successful LACI on 12 Mar 02, for ischemia in the left leg. Restenosis necessitated reintervention on 24 Jul 02. This event was related to the LACI procedure.
LEI 005 RUERO	This 58 year old female underwent LACI on 6 Feb 02, with procedural success in the right leg. However, reintervention was necessary on 28 Mar 02, due to non-healing ulcerations. This event was related to the LACI procedure.
LEI 028 ECUMA	On 17 Apr 02, this 76 year old woman was unsuccessfully treated, using LACI, in the left leg. A non-occluding distal embolism was noted during the procedure, probably related to stent placement. Thrombolysis was successful and the patient was released on the next day. This event has been judged as relevant to LACI.
MAN 009 KEHCH	On 3 Apr 02, an 85 year old male received successful LACI treatment in his left leg. Re-use of the LACI procedure was necessary due to re-occlusion of the SFA on 19 Sep 02. This event has been adjudicated as relevant to LACI.
RIV 001 BARDA	A male patient, 73 years old, was treated on 6 Aug 01. Procedural success was achieved in the right leg. Advanced gangrene necessitated a below the knee amputation on 17 Sep 01. This amputation is considered to be related to LACI.
RIV 003 HERGW	Successful treatment was noted for this 63 year old woman, even though the laser catheter did not pass the stenosis in her right leg, on 15 Aug 01. On 1 Nov 01, physicians reintervened including balloon angioplasty and stent placement. This event has been adjudicated as relevant to LACI.
RIV 004 SECAR	A male patient, 82 years of age, received successful LACI intervention, in the left leg, on 22 Aug 01. After about 3 months, on 31 Oct 01, the investigator performed repeat angioplasty to open vessels, in an effort to promote healing of minor amputations of left toes. This event was judged as relevant to LACI. (Please refer to death narrative above.)
SJO 001 DUBFR	Female patient, 84 years old, received successful LACI treatment on 16 Oct 01, for ischemia in the left leg. Prior to 6 month follow the patient experienced reocclusion in conjunction with an enlarging ulcer. On 17 Feb 02, repeat laser atherectomy and stent placement was deemed necessary. This event was later adjudicated as an SAE.
SJO 003 CULAG	On 3 Jan 02, a female diabetic patient 78 years of age, was unsuccessfully treated for stenosis on the right leg. Bypass surgery on 21 Jan 02, was reported in conjunction with the 1 month follow-up on 25 Feb 02. The patient suffered complications including heart failure (see above), and died on 10 Feb 02.
SJO 005 BOYRO	A 55 year old female patient was treated on 12 Mar 02. Procedural success was not achieved in the right leg. A below the knee amputation became necessary on 8 May 02. This event has be adjudicated as related to LACI.
SJO 006 NOODA	A 56 year old diabetic male patient presented with critical ischemia in the right leg, and was treated on 21 Mar 02. In spite of procedural success, the patient experienced reocclusion, and repeat angioplasty was necessary on 8 Jul 02. This reintervention was later adjudicated as an SAE.

	ADJUDICATED "TRUE" LACI SERIOUS ADVERSE EVENTS (NON-DEATH) RELATED TO LACI PROCEDURE – REGISTRY GROUP CONTINUED
WHC 001 SMIJO	A 75-year-old woman was treated successfully on 18 Oct 02, using the LACI technique on the left leg. The treatment site reoccluded, requiring reintervention between 1 Nov and 14 Dec 01. This event was adjudicated as relevant to LACI.
ZEL 004 PRZOL	The investigator achieved procedural success in the right leg of a 73 year old female, during a LACI intervention on 14 Jan 02. Reintervention was necessary on 18 Apr 02. This event is considered to be related to LACI.
ZEL 013 TSCER	Procedural success was not achieved during LACI intervention in the left leg of a 68 year old woman, on 22 Feb 02. Investigators noted restenosis on 7 Aug 02, and hospitalization for reintervention was required between 6 Aug, and 12 Aug 02. This event is adjudicated as related to LACI.
ZEL 014 SAMRO	This 75 year old male patient was successfully treated for ischemia in the right leg on 25 Feb 02. Hospital officials readmitted him between 18 Jun, and 21 Jun 02, due to restenosis. This event is adjudicated as related to LACI.
ZEL 016 EBEAN	Doctors successfully intervened, and reopened stenoses in the right leg of a 73 year old female on 11 Mar 02. Reocclusion required reintervention between 16 Jun, and 17 Jun 02. This event was adjudicated as related to LACI.
ZEL 017 BRUHI	A 76 year old woman received LACI treatment on 21 Mar 02. The intervention successfully opened stenoses in her left leg. An above the knee amputation was necessary on 9 Sept 02, due to continued sepsis. This incident has been adjudicated as relevant to LACI.
ZEL 019 SEUHA	On 8 Apr 02, a 73 year old diabetic male patient was unsuccessfully treated using LACI, on the right leg. On 14 May 02, repeat angioplasty was necessary. This reintervention was later adjudicated as an SAE.
ZEL 020 ZIPAD	This male patient, 68 years of age, was treated on 8 Apr 02. LACI procedures successfully opened stenoses in his right leg. Physicians performed an above the knee amputation, due to continued infection, between 27 Apr 02, and 29 Apr 02. This amputation is considered relevant to LACI.

	ADJUDICATED "TRUE" LACI SERIOUS ADVERSE EVENTS (NON-DEATH) UNRELATED TO LACI PROCEDURE – REGISTRY GROUP
GRE 019 GRAWI	SAE #1 – An 88-year-old diabetic woman presented on 17 Apr 02 with Rutherford category 5 critical ischemia, and received LACI treatment on the left leg. LACI was not procedurally successful. Rehospitalization was necessary between 4 May 02, and 16 May 02 for dysphagia. This was adjudicated as a true SAE, but unrelated to LACI. SAE #2 – Prolonged hospitalization was necessary again between 16 May 02, and 31 May 02 for endurance conditioning and family education. This was adjudicated as a true SAE, but unrelated to LACI. Note: SAE's reports #3 and #4 are of record for this patient, but have been adjudicated and non-SAE's.
AHI 004 WATG	This 83-year-old woman suffered from on-going gangrene in lower right extremities. She was hospitalized around the time of her 6-month follow up between 18 Dec 01, and 28 Dec 01, during which a below the knee amputation was necessary. This serious adverse event (SAE) has been adjudicated as related to the LACI procedure, carried out 10 Sep 01. The patient's death due to congestive heart failure (see above) was adjudicated as not related to LACI.

	ADJUDICATED "TRUE" LACI SERIOUS ADVERSE EVENTS (NON-DEATH) RELATED TO LACI PROCEDURE - TRAINING GROUP
SJO T02 RIOMA	Woman, 74 years old with diabetes, was screened on 20 Sep 02 with ulcerations on the left extremities, Rutherford category 5, and total occlusions. Occlusions were not re-opened with either laser or balloon angioplasty catheters. Investigators decided to perform a below the knee amputation on 18 Oct 01. This event has been adjudicated as relevant to LACI. (See SAE death narrative above.)
SLM T01 WAIES	Woman with diabetes, 77 years old, presented with Rutherford category 5 ischemia on 10 Jul 01, and was successfully treated using LACI procedures on the right leg. Bypass surgery was noted on the 1-month follow up, dated 7 Sep 01.

7. Discussion

Patient characteristics and procedural results

The Registry Group patient descriptors were similar to the Control Group in both age and history of smoking.

However, more women and more comorbidities were noted in the Registry Group, including more hypertension, prior stroke, diabetes, hypercholesterolemia and obesity. More current smokers were treated in the Control Group. None of these variables correlated with mortality or major amputation.

In LACI, 71/155 limbs were treated in patients with ASA Class 4. It appears that the control publication does not report the number of control patients with ASA Class 4. However, the publication does give some relevant statistics in the last paragraph on page 415 of the article. Of the 63% of the 789 enrolled control patients who did not receive revascularization,

- 9.5% were ineligible for surgery due to their general clinical condition, and
- an additional 7.5% were ineligible due to both their general clinical condition and their peripheral vascular condition.

Thus 9.5% + 7.5% = 17% of the nonrevascularized subset, or 17% X 63% = 10.7% of all enrolled patients, had a general clinical condition that precluded revascularization. If a "general clinical condition that precluded revascularization" is similar to ASA Class 4, then LACI can be compared to the control group as follows:

Table 22 Proportion high-risk patients

LACI ASA Class 4	Control patients with general clinical condition that precluded revascularization	Dif [95% CI]
66/145 (46%)	84/789 (11%)	35% [27%, 44%]

In this comparison, significantly more of the LACI population had a poor clinical condition. Overall the Registry Group was a more morbid patient group.

CLI presentation was similar between the Registry Group and the Control Group, with the same ratios of Rutherford Category 4 (rest pain without ulcers) and Category 5-6. In the Registry Group, Category 6 was a univariate predictor of major amputation.

Lesion characteristics describe a vascular disease condition that is widespread and severe. Treatment was needed over a long length of each leg, starting typically in the thigh and

extending in many cases to the ankle. On average each leg was treated at 3 places in the index procedure. Arteries were typically highly stenosed or occluded.

Delivery of laser treatment was successful in all but 2 Registry Legs. (In these two cases, the guidewire could not cross the lesion(s) and so the procedure was aborted.) Angiographically, laser debulking contributed about half of the total luminal gain seen in the minimum %DS (% diameter stenosis) statistics, but this does not well reflect the debulking that occurred along the length of the artery, proximal and distal to the point of minimum lumen diameter. In larger arteries where stenting was more prevalent, such as the SFA or popliteal, a lower mean final %DS was achieved. The overall objective was to achieve "straight line flow" to the foot, that is, a patent channel from the common femoral artery, through the popliteal, and continuing through at least one of the infrapopliteal arteries (anterior tibial, posterior tibial, or peroneal). This objective was achieved in 89% of Registry Group patients.

Angioplasty or thrombectomy was delivered to 7.5% of the Control Group, but statistics on lesion characteristics or procedural outcomes were not included in the publication.

Control Group patients stayed in the hospital for a mean of 23 days, compared to a mean of 3 days (median: 1 day) for the Registry Group.

Comparison of endpoints

Freedom from major amputation and survival at 6 months was nonsignificantly higher in the Registry Group, compared to the Control Group.

In the Registry Group, procedural complications comprised events typically observed during peripheral atherectomy. Dissections and perforations, though few, were treated with prolonged balloon angioplasty and stenting. Embolization of thrombus was treated successfully with standard therapies. No vascular surgical intervention was required secondary to a treatment complication. In-hospital complications also conformed with expectations, with the most frequent observation being groin bleeding treated without surgery.

In-hospital SAEs were minimal, comprising 3 events (2% of patients) in the Registry Group. By comparison, in the Control Group, primary amputation was the treatment for 9.6% of patients; another 30% received a bypass operation, and 5% received (surgical) endarterectomy.

Effectively equivalent results were achieved in the Registry Group with markedly lower incidence of surgery, which was the basic premise of the LACI protocol.

For both the primary efficacy endpoint (limb salvage, or freedom from major amputation) and the primary safety endpoint (survival), the LACI hypothesis was non-inferiority. The LACI data support this hypothesis.

The ICAI control group was chosen primarily because the Control Group statistics represented the best clinical outcome that one could hope to achieve in CLI patients. LACI proved to be as safe and effective, *for the purpose of limb salvage,* as the best possible care given to CLI patients

(in fact, given to a CLI patient population that presented in the Control Group with less comorbidity than LACI patients). This justifies the use of the CVX-300 Excimer Laser System in CLI patients who are poor surgical candidates, for the purpose of limb salvage.

Alternative Treatments

The key to understanding the positive risk/benefit profile of LACI is understanding what alternatives LACI patients (patients presenting with CLI who are poor surgical candidates) face in the absence of LACI. LACI patients would likely receive either primary amputation or medical (conservative) therapy if LACI were not available. This treatment strategy is different from the LACI control group strategy, in which surgical bypass was a key feature. Fortunately the literature provides benchmark values of patient outcomes for treatment strategies that LACI patients might receive.

The cornerstone concept on which the LACI protocol is based is that limb salvage has greater benefit to the patient than major amputation. A great body of medical literature to supports this concept. Over the last 30 years, as data became available on the benefit of revascularizing limbs with CLI, the realization of the relative benefits of revascularization became so profound that direct comparisons with amputation became difficult. One author (22) noted, "…at the present time [1988] a randomized study comparing the two treatment modalities [amputation and revascularization] is not feasible." Hence the comparative literature on amputation is largely based on retrospective studies, usually from a single site.

In 1988, Ouriel (22) compared amputees against revascularized patients. He also further classified the patients into Class A (Goldman score <5 and ASA class I or II), Class B (Goldman score 5-9 or ASA class III), Class C (Goldman score >9 or ASA class IV or V). Perioperative mortality was significantly greater for below the knee amputations than for revascularization (7.6% vs 2.9%, $p<0.05$). However, in Class C patients the difference was even more dramatic, 16% for amputation vs. 6% for revascularization. Length of hospital stay was reported as 14 ? 2 days on average for revascularization and 31 ? 3 days for amputation. Full ambulatory status was regained by 72% of Ouriel's Class C revascularization patients, but only 44% of the Class C amputees. The Class C revascularization patients had a long term survival rate of 76%, while 29% of Class C amputees survived after 3 years ($p<0.001$). These data "reiterate the augmented mortality of amputation and promulgate the concept of an aggressive approach to lower-extremity vascular reconstruction, irrespective of medical status."

In comparing the quality of life (QOL) for patients who were revascularized against those with primary amputation, Thompson (23) found no significant difference between the groups in anxiety, but the revascularized group was significantly lower in depression and impairment of social function and had significantly greater mobility. Further, QOL of the revascularized group was unaffected by a reintervention, and there was no difference in QOL between primary amputation patients and patients who received amputation after a failed revascularization. **QOL was always higher in patients with limb salvage**. This author concluded that "repeated interventions to maintain graft patency, either thrombectomy of a failed graft, or radiological or surgical angioplasty to treat vein graft stenoses, did not adversely affect the quality of life of patients following infragenicular arterial reconstruction."

In an article reporting five year follow-up of socioeconomic outcomes, Luther (24) found that amputation of a previously mobile patient cost twice as much as reconstruction on a cost/year basis, including those followed with a later amputation. Costs for amputation of a non-institutionalized patient were 114% higher than for any type of reconstruction and 220% higher than for a successful reconstruction, which was similar to the costs for reconstruction followed by later amputation. Luther found "no economic reason to perform an amputation in preference to a reconstruction on independently living patients. For these patients, preserved mobility and the quality of life should be the main factors in deciding on leg salvage attempts through a reconstruction. For the immobile patient already in institutional care where CLI constitutes a care problem, an amputation is often an inevitable and expensive solution."

In Pomposelli's (25) article on lower extremity reconstruction in the very elderly, he found that for patients at least 80 years old with reconstructed limbs, survival rate was nearly twice that of patients who had undergone major amputation: 44% at five years vs. 28% at four years. In the amputation group 55% got "a lot worse" as far as independent function and 35% got worse as far as residential status. Revascularized patients improved or remained the same in 78% and 88% respectively. Thus even patients of advanced age benefited from revascularization rather than amputation.

Kalra (26) found primary amputation to have a high mortality rate (13-17%) and only two-thirds of the survivors were successfully rehabilitated. For cumulative survival at one, three and five years the surgical revascularization patients had rates of 87%, 76% and 60% respectively. The primary amputation patients had rates of 79%, 52% and 26% for the same periods. Amputation was a significant independent risk factor, predicting a higher long-term mortality rate on multivariate analysis.

In a brief review of data, Muluk (27) recognized that while advances in vascular surgery have made it possible to salvage limbs that might otherwise have been amputated, this does not justify the limb salvage in every case. He suggested that revascularization is inappropriate for the bedridden, elderly patient unless ischemia is the cause of their nonambulatory status. He further stated, "it should be noted that amputation does not necessarily carry any lower risk than revascularization in the elderly, poor risk patient. There can be no substitute for individualized decision making, but large series have shown that more than 85% of patients who have undergone aggressive attempts at limb salvage retain their limbs until death. Furthermore, although the cost of revascularization is high, so too is the cost of amputation and rehabilitation, or amputation followed by chronic bedridden status."

In a book on Critical Limb Ischemia, Robinson and Beard (28) agreed,for people with the poorest preoperative function level, limb salvage was not justified as a means to preserve mobility. The authors noted that most patients, when given a choice, will choose revascularization, however for those in whom mobility is not a priority, amputation may be the best choice. They commented that the patient's perception of life is the most important determinant in the decision, "there are patients who adapt to loss of limb with little apparent concern just as there are those for whom amputation seems incompatible with living." This leads to the conclusion that the decision to perform revascularization or primary amputation should be based on what is best for the individual patient.

In a recent editorial Nehler (29) expresses concern that CLI is not well enough understood to assume revascularization is the best treatment for most patients. These patients have many comorbidities that affect outcome, but the extent is not yet well comprehended, nor are they necessarily taken into consideration when making the treatment decision. The authors offer the suggestion of approaching the decision of amputation vs. revascularization from a three-sided view: technical issues, foot wound healing issues and comorbidity. They suggest, as have several others, that amputation is the best choice for a home-bound patient with large gangrenous wounds or for the patient who cannot be expected to survive the follow-up required to heal those wounds.

While these articles cover several years of research they have similar themes: revascularization has longer survival rates and lower cost than primary amputation. Independent patients of any age may best be served by maintaining mobility and independence with limb salvage. However, revascularization is not the appropriate treatment for all CLI patients. Some groups of patients (the bedridden, immobile or terminally ill) may best be served by primary amputation to alleviate the pain of CLI. The decision to revascularize should be made with the patient's best interest in mind. The pervasiveness of this treatment philosophy was tested in the Delphi Consensus Study (30), in which a variety of physicians were presented with 596 different hypothetical CLI patient scenarios with a wide range of disease severity, anatomic extent, coexistent conditions, etc. "Both surgeons and radiologists thought primary amputation was indicated in approximately 9-10% of the scenarios." **That is, primary amputation should be reserved for only the most hopeless of cases. This is the concept on which the LACI protocol was based.**

One might ask, if the LACI statistics are no better than the control, why treat CLI patients with the LACI strategy, if they can enjoy equivalent results with the treatment strategy employed in the control group? The answer is that LACI patients, being poor surgical candidates, cannot be treated with the strategy employed in the control group. An integral part of the control group treatment strategy was bypass surgery or endarterectomy (given to 35% of control group patients) whereas surgery is not recommended for LACI patients. To show that LACI has a positive risk/benefit profile, LACI results should be compared to the treatment strategies that they would have received in the absence of LACI treatment.

LACI vs. Primary Amputation

It might be proposed that primary amputation might better serve LACI patients who were not at increased risk for surgical mortality, that is, who were not ASA Class 4 or above. To check this possibility, an analysis of a subset of LACI patients who were not ASA Class 4 or above was compared to literature values. Four articles with relatively large case series (>100 subjects) and statistics on follow-up required for the comparisons were chosen and included in Table 2. Table 2 shows remarkably long hospital stay for amputation, about 3 weeks, compared to 2.6 days for LACI. Perioperative mortality ranges from 1% to 11% for amputation, whereas none was seen in LACI. Death at 6 months was also higher for amputation. Reintervention (conversion from BKA to AKA) was required in 19% of amputations, whereas a second angioplasty was required in 15% of LACI cases. If only deaths and conversion of BKA to AKA

are considered as serious adverse events (SAEs) for the amputation groups, then the amputees had a total SAE rate comparable to LACI, wherein most of the SAEs were re-angioplasties. The only benefit that might accrue to the primary amputation group is lack of persistent CLI, but this conclusion is somewhat clouded by the presence of up to 11% unhealed stumps at 6 months. One could argue that amputation does not totally remove nonhealing wounds, which would classify a pre-amputation patient as having CLI. **In summary, LACI benefits include limb salvage, shorter hospital stay, no perioperative mortality, and lower reintervention, while risks are no higher and of less serious types.** Primary amputation has lower persistent CLI, but no other outcome favors primary amputation over LACI.

Table 23 Outcomes for LACI patients not ASA Class 4 or above, compared to amputation patients

	LACI - Not ASA Class 4 or above	Rush et al, 1981 (31)	Dormandy et al, 1994 (32)	Ouriel et al, 1988 (33)	Bunt et al, 1984 (34)
N, patients	84 (100%)	135 BKA 121 AKA	713 BKA	158 BKA	113 BKA 140 AKA
Hospital stay, days	2.6 ? 5.3 days	22 BKA 36 AKA	33**	19	
Perioperative mortality	0	6% BKA 11% AKA	1%	7.6%¤	1% BKA 3% AKA
Outcomes at Follow-Up					
Limb salvage	69 (82%)	0%	0%	0%	0%
Persistent CLI	28 (33%)	0%	11% unhealed stumps		0%
Death	5 (6%) (within 6 months	21% BKA* 34% AKA*	11%***	8%	
Reintervention	13 (15%)	19% BKA to AKA	19% BKA to AKA		
Major amputation	7 (8%)	100%	100%		
Total SAEs	30 (36%)	?34%	?30%		
		*12 months	**among those pts discharged by 3 months ***3 months	¤30 days	

LACI vs. Medication

It might be suggested that medication and bed rest would be the most probable treatment strategy for patients in ASA Class 4 or above, in the absence of LACI. To check this possibility, results in a subset of LACI patients who were ASA Class 4 or above were compared to literature values. Three articles were chosen for comparison based on large case series (>100 subjects), with 6-month follow-up statistics, published within the last 10 years. Also, These publications focused on subjects who were not good surgical candidates, so that the subjects would be similar to LACI.

Table 3 shows that conservatively treated patients typically have an initial hospital stay at least 10 days longer than LACI. Limb salvage rates are lower than LACI, by at least 10% absolute. Death at 6 months varies widely, and was lower than LACI in one report and higher than LACI in the others. Major amputation was given to at least 37% of conservatively treated patients, compared to 6% of this LACI subset. The incidence of surgical bypass was also higher, presumably as a desperate measure in patients who are poor surgical candidates. Assuming that death, bypass, and major amputation are SAEs for the conservatively treated groups, total SAEs are much higher in the conservatively treated groups than in LACI. In summary, the outlook for conservatively treated patients is dismal**. LACI provides benefit and reduced risk in all outcomes.**

Table 24 Outcomes for LACI patients in ASA Class 4, compared to patients treated conservatively

	LACI ASA Class 4 or above	UK SLI Group, 1991 (35)	Norgren et al, 1990 (36)	Lepantalo et al, 1996 (37)
N, patients	71 (100%)	151	103	105
Hospital stay, days	3.4 ? 4.8	14-28	>14	
Perioperative mortality	0			
Outcomes at 6-month Follow-Up				
Limb salvage	49 (69%)	52%		58%
Persistent CLI	15 (21%)	No CLI in 26%		
Death	10 (14%)	8%	13%	42%
Major amputation	4 (6%)	37%	38%	
Surgical bypass	1 (1%)	11%		
Total SAEs	28 (39%)	?48%	?51%	?42%

LACI vs. PTA

One could ask if PTA (without excimer laser atherectomy) could be used to treat the patient population enrolled in LACI. The TASC Document, which is the authoritative medical definition of the clinical and scientific principles on which LACI was based, has specific recommendations on treatment modalities, based on the patient's anatomic disease pattern (see: TransAtlantic Inter-Society Consensus (TASC) on Management of peripheral arterial disease (PAD). J Vasc Surg 2000; 31 (1, Part 2) 1-296). TASC recommends that PTA be used only in CLI patients with single, focal stenoses <1 cm. For patients with extensive and severe disease, such as those enrolled in LACI, PTA was not recommended. There are many literature reports of PTA in CLI, but virtually all of these are retrospective analyses of patients chosen for PTA based on selection criteria thought at the time to be favorable to PTA. Finding reports of PTA in populations comparable to LACI proved to be challenging. Several reports published in the last 8 years with case series of at least 50 patients with CLI in at least 90% of patients and follow-up data to at least 6 months were identified.

Comparisons in Table 4 exemplify the difficulty in finding reference data on CLI patients who are poor surgical candidates. The investigators cited in the table selected their patients for PTA based on their respective in-house suitability criteria during the time period of each study. That is, they selected patients with anatomic criteria thought to have favorable outcomes with PTA and not on their candidacy status for bypass surgery. By contrast, LACI enrolled virtually all patients who were poor candidates for bypass surgery, regardless of the anatomic complexity of their vascular disease. This is evidenced by the long total treated lesion length and the high number of treated lesions per limb in LACI.

The article by Dorros typifies the difficulty of comparing LACI results to literature references. In the Dorros article, only patients selected for PTA are included; acute procedure success was be granted even when the final minimum lumen percent diameter is <50%; lesions per limbs and length of treated artery per limb are not stated; acute and in-hospital success is never stated on a per-patient basis or on a per-limb basis; reinterventions are not mentioned at all; and long-term results are computed only for those patients with successful revascularizations. Despite these limitations on reporting, the article shows that, if PTA is successful in CLI, in-hospital complications are infrequent and the limb salvage rate can be quite high. It must be stressed that the basis on which the results are computed in the Dorros article is not comparable to LACI, and there is no reliable way to determine if the enrolled patient populations are similar between Dorros's study and LACI.

Taking the outcomes mentioned in the table at face value, it is evident that the frequency of reintervention in LACI was only marginally higher than in the cited publications, but the incidences of bypass and major amputation were noticeably lower in LACI than in the cited publications. Apparently the marginally higher reintervention in LACI facilitated higher limb salvage and freedom from bypass. Overall the results show that the LACI treatment strategy, as applied to a fragile patient group with very extensive peripheral vascular disease, is at least as effective as the reference values for PTA in patients selected with simpler disease patterns known to be amenable to PTA. **The clinical advantage of the LACI strategy is that a single intravascular regimen used in LACI achieved a lower rate of major amputation in a more extensively diseased population, than PTA did in simpler disease patterns.**

Table 25 Outcomes for LACI limbs and for PTA in CLI patients.

	LACI 2	Soder 2000 (38)	Lofberg 1996 (39)	Matsi 1994 (40)	Danielsson 2001 (41)	Dorros 2001 (42)
Treated during	2000-01	1996-7	1989-93	1989-92	1990-97	1983-96
Pts/limbs	145/155	60/72	82/86	103/117	140/155	235/284
CLI	100%	100%	100%	100%	90%	100%
Pt selection	All poor surgical candidates	Selected for PTA	Selected for PTA	Selected for PTA	Selected for PTA	Selected for PTA; results on successful PTA only
Total treated length	16.2 cm	3.8 cm	-	10.6 cm	-	
Lesions/limb	2.7	2.6	2.3	1.8	1.5	2.3
Reintervention	15%‡	11%‡	12%†	9%†	10%†	
Bypass	2%‡	-	15%†	7%	6%†	8%ª
Death	10%‡	25%†	17%†	9%*	15%†	10%†
Major amputation	7%‡	17%†	19%‡	21%*	10%†	9%ª

*30 day ‡6 months †1 year ª5 year, initial successes only

LACI vs. Bypass Surgery

One might expect to place bypass surgery in the position of being the "gold standard" for treatment of CLI. While bypass surgery is not a reasonable treatment option for LACI patients

(who were selected because they were poor surgical candidates), it might be chosen in desperation prior to an amputation that was nearly inevitable. To check if LACI has advantage over expected outcomes in patients treated with bypass, literature references on bypass surgery were selected for comparison. The literature chosen for this comparison represent critically ischemic patients treated with current bypass standards, in a population treated between 1987 and 2000. The cited bypass strategies and anastamosis site selections are most suitable for the atherosclerotic disease pattern typically seen in this patient population. (43,44) Additionally, all procedures cited were performed using the preferred conduit for infrainguinal revascularization, i.e. an autogenous vein graft instead of the less effective prosthetic graft. (45,46)

Table 26 Outcomes for LACI limbs and publications on the use of bypass in CLI patients.

	LACI 2	Pomposelli (47) 2003	Toursarkissian (48) 2002	Curi (49) 2002 (GSV arm of study)	Kalra (50) 2001
Treated during	2000-01	1990-2000	-	1995-2000	1987-1998
Pts/limbs	145/155	865/ 1032	64/ 68	239 bypasses	256/ 280
CLI	100%	100%	100%	LS attempt in 91%	100%
Pt selection	All poor surgical candidates, 66% diabetic	92% diabetic	100% diabetic	62% diabetic	74.6% diabetic
Graft type; placement		99.8% autogenous; DP	94.1% autogenous; infrainguinal	100% autogenous; infrageniculate	100% autogenous; DP
Follow-up timeframe	6 months	23.6 months (1 – 120)	12 ? 6 months (1-26)	18 months (0.1-79)	2.7 yrs (0.1-10.1)
Reintervention/ graft revision w/in 30 days	2 (1.3%)	71 (7.9%): 13 (1.3%) revisions plus 68 (6.6%) underwent unexpected early reoperation	-	-	9 (3.2%)
Reintervention/ graft revision during follow-up	22 (14.2%)	-	13 (19.1%), at a mean of 4 ? 3 months	-	23 (8.2%)
Bypass	2%	100%	100%	100%	100%
Death	0%* 10%‡	1.0%* 51.4% at 5 yrs	-	2.1%* ~25% at 4 yrs	1.6%* 30.2% during f-up
Major amputation	7%‡	78.2% LS at 5 yrs	11.8%	4.6%*	18.2%

*30 day ‡6 months †1 year
LS = Limb Salvage, DP = Dorsalis Pedis, GSV = Greater Saphenous Vein

Although direct comparison between the LACI poor surgical candidate population and bypass surgical patients is difficult, the early in-hospital complications, including reintervention and death at 30 days, favor LACI. Long term outcomes, including death and major amputation, are similar among the studies cited in Table 5.

Comparative Summary of Treatment Options for CLI

In summary, LACI showed a distinctly better risk/benefit profile than the two treatment options currently available to LACI patients -- medication or primary amputation. Bypass surgery, the "gold standard" for CLI, is not a good option for LACI patients, and yet LACI achieved limb salvage comparable to the "gold standard" of bypass surgery, without higher SAEs. The LACI treatment regimen showed results at least as good as large case series of PTA in CLI, despite the fact that LACI enrolled patients with far more extensive disease.

The justification for using LACI to treat CLI patients who are poor surgical candidates lies in its clinical benefit. LACI results showed greater benefit vis-à-vis any treatment strategy this patient cohort might have expected. LACI risks were lower than or not inferior to any treatment strategy this patient cohort might have expected. In fact, LACI results showed the same benefit as the best treatment strategy given to CLI patients who were (in the vast majority) good surgical candidates. LACI treatment provides an effective alternative for limb salvage in a patient population currently lacking options.

Study limitations

LACI Phase 2 was limited by several factors:

?? The study used a historical control and was not randomized.
?? Different centers were used in LACI than in the Control Group. Standards of care likely differed the two studies.
?? LACI Phase 2 was not sized to power statistical comparison between subgroups.
?? During the index procedure, multiple treatments were typically delivered in sequence (e.g. laser atherectomy, balloon angioplasty, optional stenting). Also, several arteries were typically treated during the index procedure. However, the primary outcome measured the effect on the entire limb (that is, limb salvage). LACI was not designed to separate the effects of individual treatment modalities and of treating individual arteries.

8. Study in progress

At the time this report was written, there was no study in progress using ELA on CLI patients.

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10. Limb Listing

The following 4 pages contain a listing of enrolled legs for All Patients.

11. Additional Clinical Studies (LACI Phase 1)

An initial clinical study, LACI Phase 1, enrolled 25 limbs. The primary endpoint of the LACI Phase 1 protocol was wound healing at 3 months. Secondary endpoints included limb salvage and death at 6 months. A publication describing the results of LACI Phase 1 is included in Appendix 2.

Appendix 1. ICAI Study Group paper

ICAI Study Group. Prostanoids for Chronic Critical Leg Ischemia: a randomized, controlled, open-label trial with Prostaglandin E1. Ann Intern Med 1999; 130:412-421

(10 pages)

Appendix 2. LACI Phase 1 Publication

Gray BH, Laird JR, Ansel GM, Shuck JW. Complex endovascular treatment for critical limb ischemia in poor surgical candidates: a pilot study. J Endovasc Ther 2002; 9:599-604

(6 pages)

Appendix 3. Investigational Sites

Appendix 4. Digital Morphology Examples